July 28, 2025
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Program 2, Software for treatment of diseases
Term Name	Software for insomnia
Brand Name	SUSMED App for Insomnia Medcle
Applicant	Susmed, Inc.
Date of Application	August 30, 2024 (Application for partial change approval)

Results of Deliberation

In its meeting held on July 28, 2025, the Subcommittee on Software as a Medical Device of 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 Council.

The product should be approved with a designation as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

The use-results survey period should be 4 years and 6 months. The following approval conditions should be attached.

Approval Conditions

1. The applicant is required to ensure that the product is used only by physicians with adequate knowledge of insomnia, based on a thorough understanding of cognitive behavioral therapy for insomnia (CBT-I) and the product characteristics. To this end, necessary measures, including dissemination of the proper-use guidelines jointly developed with the relevant academic societies and provision of training programs, should be taken.

The intended use or indication should be changed to “to provide support for the treatment of insomnia.”

Review Report

July 17, 2025
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	Program 2, Software for treatment of diseases
Term Name	Software for insomnia
Brand Name	SUSMED App for Insomnia Medcle
Applicant	Susmed, Inc.
Date of Application	August 30, 2024
Items Warranting Special Mention	
Reviewing Office	Office of Software as a Medical Device
Remarks for Review	

Review Results

July 17, 2025

Classification	Program 2, Software for treatment of diseases
Term Name	Software for insomnia
Brand Name	SUSMED App for Insomnia Medcle
Applicant	Susmed, Inc.
Date of Application	August 30, 2024

Results of Review

"The SUSMED App for Insomnia Medcle" (hereinafter referred to as "the SUSMED App" or "the product") is mobile device application software for patients with insomnia, approved on February 15, 2023. The SUSMED App provides functions based on the approaches practiced in cognitive behavioral therapy for insomnia (CBT-I). At the end of the review for the initial marketing approval, the intended use or indication for the product was proposed as "to perform cognitive behavioral therapy for the treatment of insomnia." However, after the review at the Subcommittee on Software as a Medical Device of the Committee on Medical Devices and *In-vitro* Diagnostics, it was revised "to support cognitive behavioral therapy by physicians in the treatment of insomnia." At a subsequent review by the Central Social Insurance Medical Council on January 17, 2024 based on the intended use or indication for the initial approval, the product was excluded from insurance coverage. Recently, the applicant has filed an application for the product to be introduced as a distinctive treatment option from current pharmacotherapies or face-to-face CBT-I.

The applicant submitted non-clinical data on the SUSMED App, namely, usability engineering process and cybersecurity data. The review revealed no particular concerns.

The applicant submitted the data from a comparative analysis (the comparative analysis) with the following studies: Study SYK02 that evaluated the effectiveness of therapy using the SUSMED App, and Study S02, a clinical study that examined the effects of zolpidem tartrate as standard of care pharmacotherapy in Japan.

Unlike a parallel-group study that directly compares the SUSMED App and zolpidem tartrate, the comparative analysis employed the data from Study S02 as external control to assess the results

from the active group with the SUSMED App in Study SYK02. Consideration is seen for the possible bias in Study S02 used as external control, which is understandable. At the same time, there were some limitations in the evaluation design that hindered the discussion on superiority or inferiority of the SUSMED App to insomnia medications in efficacy and safety based on the comparative analysis results submitted.

The analysis results, however, satisfactory characterized the SUSMED App and insomnia medications such as zolpidem tartrate. While zolpidem tartrate, commonly prescribed for patients eligible for the SUSMED App, was suggested to exert an immediate effect, the SUSMED App was shown to have sustained efficacy even after treatment completion. This is considered attributable to the product's CBT-I-based design, which helps adjust patients' mindset and behaviors. Because this finding is consistent with the reports from face-to-face CBT-I, the SUSMED App has high potential for long-term efficacy even after treatment completion. Taken together, treating insomnia with the SUSMED App alone is clinically meaningful to a certain extent for patients who do not require immediate improvement.

Given the promising long-term efficacy and no safety concerns leading to an immediate problem, it is possible to regard the SUSMED App as a new treatment option for patients with insomnia poorly managed through sleep hygiene education alone, as for those receiving pharmacotherapy. It is important to continuously adhere to the proper use guidelines provided by the relevant academic societies at the initial approval and to gradually increase the number of physicians who handle the product, while assessing the proper product use training program through the newly-planned post-marketing surveillance.

As a result of its review, PMDA has concluded that the SUSMED App may be approved for the intended use shown below, with the following approval conditions, and that the application should be deliberated at the Subcommittee on Software as a Medical Device.

Intended Use

To support insomnia treatment

Approval Conditions

The applicant is required to ensure that the product is used only by physicians with adequate knowledge of insomnia, based on a thorough understanding of CBT-I and the product characteristics. To this end, necessary measures, including dissemination of the proper-use guidelines jointly developed with the relevant academic societies and provision of training programs, should be taken.

Review Report

July 17, 2025

Product for Review	
Classification	Program 2, Software for treatment of diseases
Term Name	Software for insomnia
Brand Name	SUSMED App for Insomnia Medcle
Applicant	Susmed, Inc.
Date of Application	August 30, 2024
Proposed Intended Use	To support insomnia treatment
Items Warranting Special Mention	

Table of Contents

List of Abbreviations

AIS	Athens Insomnia Scale
CBT	Cognitive behavioral therapy
CBT-I	Cognitive behavioral therapy for insomnia
CGI-I	Clinical Global Impressions-Improvement
CRB	Certified Review Borad
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ICSD-3	International Classification of Sleep Disorders, third edition
KSS	Karolinska Sleepiness Scale
M.I.N.I.	The Mini-International Neuropsychiatric Interview
RCT	Randomized Clinical Trial

I. Product Overview

"The SUSMED App for Insomnia Medcle" (hereinafter referred to as "the SUSMED App" or "the product") is mobile device application software for patients with insomnia. The product provides functions based on the practices in cognitive behavioral therapy for insomnia (CBT-I). Table 1 shows the features of the SUSMED App.

Table 1. Features of SUSMED App

Feature	Detail
Sleep log	[redacted]
Sleep hygiene education	[redacted]
Stimulus control therapy	[redacted]
Sleep restriction therapy	[redacted] The time in bed (between bedtime and arising time) is adjusted depending on the sleep efficiency calculated from the record in the sleep log, daytime sleepiness, and the degree of adherence to the target bedtime. [redacted]
Sleepiness test	Sleepiness is checked by [redacted]
Cognitive therapy	Worries and thoughts are visualized, and reviewed according to the following steps every evening [redacted]
Relaxation	Relaxation method is implemented. Data entry or check is disabled after bedtime until waking up.
Insomnia scale assessment	Subjective insomnia severity is assessed using the 8-item AIS questionnaire. Each answer is rated by number to yielding a total score ranging from 0 to 24 for evaluation. The questionnaire is performed every 7 days using [redacted] AIS.
Push notification	A function to send messages to the patient, such as the timing of use of the SUSMED App. [redacted]
Tutorial	After completion of initial settings, how to use the SUSMED App is explained with images, etc. and [redacted]
Knowledge on good sleep	Frequently asked questions and answers are displayed.

The primary features of the SUSMED App pertain to “sleep hygiene education,” “sleep scheduling” (sleep diary and sleep restriction therapy), “stimulus control therapy,” and “cognitive therapy.” Other features include self-assessment of insomnia using a scale and a sleepiness test. The patient receives sleep hygiene education and fills out sleep logs for 7 days. Over the following 8 weeks, the patient reviews the records in every morning and evening, assesses their insomnia status using the Athens Insomnia Scale (AIS; assessment of the severity of insomnia), and sets weekly target bedtime/wake-up times (Figure 1). After 9 weeks of treatment with the product, data entry to the reviews, etc. is automatically disabled and, when starting, the SUSMED App displays a message telling the completion of use period. The product is also designed to disable data entry or check after bedtime until waking up so as to discourage prolonged use of the smart phone in bed for using the SUSMED App. Data entered by the patient are stored in the management system database.

The SUSMED App was approved on February 15, 2023 for the intended use or indication of “to support cognitive behavioral therapy provided by physicians for the treatment of insomnia.” The functions, etc. of the device have not been changed after marketing approval.

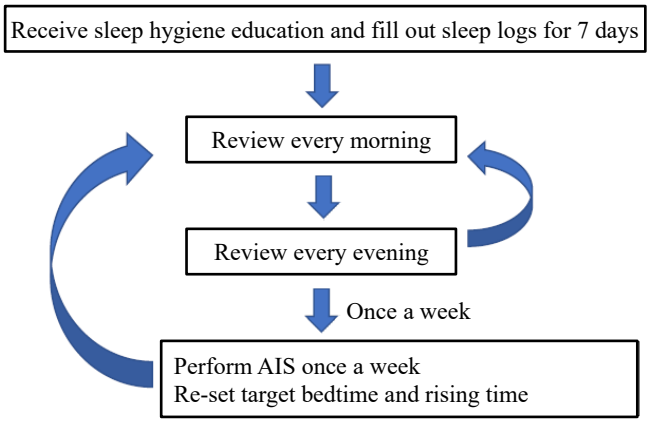

Figure 1. Eight weeks of CBT-I using SUSMED App

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

The data submitted in the present 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 the SUSMED App declared that they did not fall under 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.A Summary of the data submitted

History of development

Insomnia is a form of sleep disorder characterized by symptoms including sleep onset insomnia, nocturnal awakening, early morning awakening, and nonrestorative sleep. Insomnia is one of the most common illnesses in primary care. In the International Classification of Sleep Disorders, third edition (ICSD-3), insomnia is defined as persistent difficulty with sleep initiation, duration, consolidation, or quality occurring despite adequate opportunity and circumstances for sleep, resulting in some daytime impairment. The diagnostic criteria include the presence of insomnia symptoms and nocturnal sleeping difficulty-related symptoms, as well as sleep impairment-related daytime symptoms. In ICSD-3, the diagnosis of insomnia include both primary insomnia and secondary insomnia (sleep disorder comorbid with other conditions), which were separately categorized in the prior editions. For many years, the ICSD has been used by sleep specialists as a major classification system for sleep disorders, and the mentioned definition is also adopted in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). Thus, the definition of insomnia is common to DSM-5 and ICSD-3.

Insomnia is treated with pharmacotherapies and non-pharmacotherapies such as cognitive behavior therapy. In the "Clinical Guidelines for Proper Use and Withdrawal of Hypnotics: Manual for Insomnia Treatment With an Exit Plan"[1] (hereinafter referred to as "the Japanese Clinical Guidelines") published in Japan, with the treatment algorithm (Figure 2), cognitive behavior therapy is outlined: "Psychological/behavioral interventions should also be initiated concurrently with pharmacotherapy as early as possible where the situation permits. Although being a representative intervention, CBT-I is defined in the Japanese Clinical Guidelines as a second-line treatment for patients with insomnia inadequately responding to pharmacotherapy. However, CBT-I has been shown to be effective as a first-line treatment or in combination with pharmacotherapy as well."

In the latest European Insomnia Guideline revised in November 2023,[2] CBT-I with a programmed medical device (hereinafter referred to as "digital CBT-I") is a separate treatment option but not a part of face-to-face CBT-I offered by healthcare professionals (face-to-face CBT-I). Pharmacotherapy is regarded as a second-line therapy for patients with insomnia inadequately responding to CBT-I. In recent years, several digital CBT-I products have been approved outside Japan, and face-to-face CBT-I and digital CBT-I are independently performed.

Currently, popular treatment approaches in Japan are pharmacotherapies with sleep medications. The advantages of these drugs are immediate effect to reduce sleep onset latency and

improvement in nocturnal awakening.

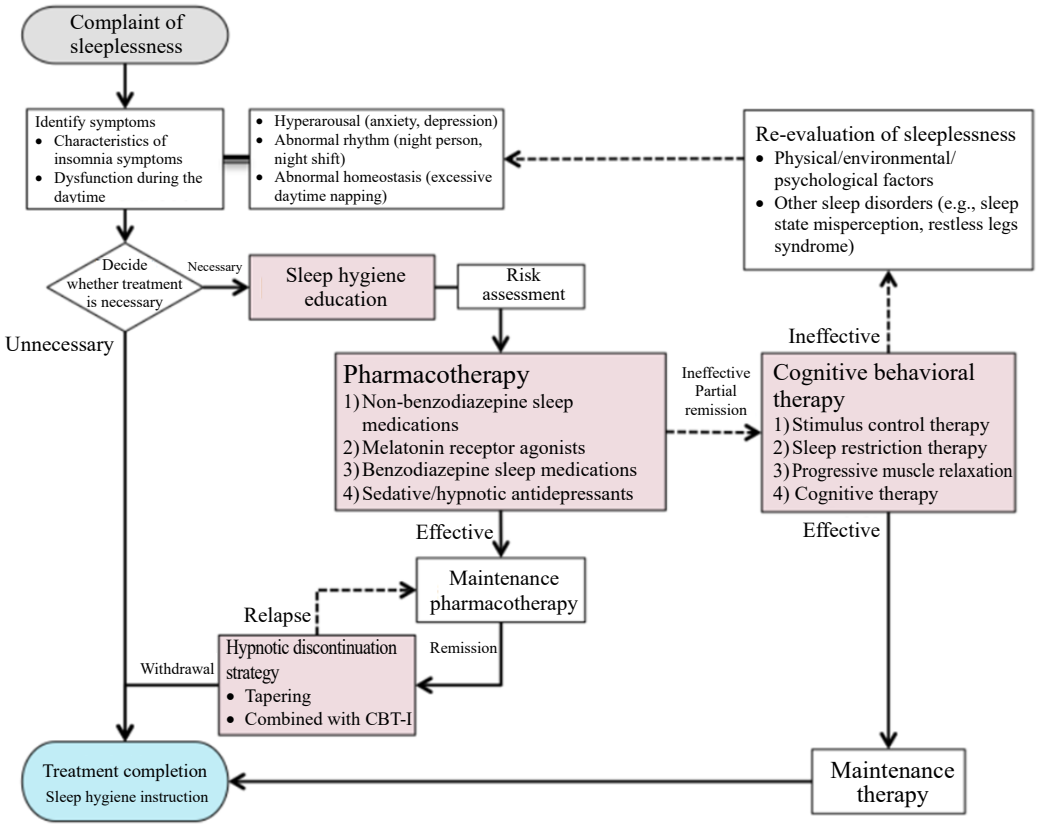

Figure 2. Treatment algorithm

At the same time, vigilance is required for “carry-over” effects of pharmacotherapies, including physical symptoms (e.g., dizziness and falls), headache, and malaise, as well as drug interactions with concomitant medications. Rebound insomnia and withdrawal symptoms after the completion of sleep medications may lead to drug dependence, and thus the use of these agents needs to be minimized. This remains a challenging issue in terms of proper use. While insomnia is a common disease, particularly non-sleep specialists have no treatment options other than sleep medications. For this reason, the reported amount of prescribed sleep medications per population is significantly high in Japan among developed countries, 6 times as high as in the US.[3]

Despite the above-mentioned issues, the percentage of prescribed sleep medication has not decreased significantly, and the issues remains unresolved.[4]

The SUSMED App is medical application software for the treatment of insomnia developed to address these issues. The product is aimed to enable medical institutions and physicians treating

insomnia, regardless of their departments or specialty, etc., to provide non-pharmacological intervention without causing further staff shortages in Japan. The applicant conducted a sham-controlled multicenter, double-blind study (Study SYK02) to evaluate the efficacy and safety of the SUSMED App. The results demonstrated the superiority of the SUSMED App over the sham app in terms of improvement as measured by AIS, a scale used to measure the severity of insomnia. Based on the results, the SUSMED App was approved on February 15, 2023. At the end of the review of the application for the initial marketing approval, the intended use or indication for the product was "to perform cognitive behavioral therapy for the treatment of insomnia." However, after being reviewed by the Subcommittee on Software as a Medical Device of the Committee on Medical Devices and *In-vitro* Diagnostics, this was changed to "to support cognitive behavioral therapy provided by physicians for the treatment of insomnia."

At a subsequent review by the Central Social Insurance Medical Council on January 17, 2024, based on the intended use or indication for the initial approval, it was decided that the product would not be covered by insurance.[5] As mentioned earlier, guidelines outside Japan reflect notions about digital CBT-I different from pharmacotherapies or face-to-face CBT-I. Therefore, the applicant decided to introduce the SUSMED App as a new treatment option distinct from pharmacotherapies or face-to-face CBT-I.

Considering that, based on data from similar overseas products and clinical research results on sleep medications, the SUSMED App would be capable of demonstrating its clinical usefulness even as an option equivalent to pharmacotherapies in Japan, the applicant submitted the application.

Use in and outside Japan

The SUSMED App has not been used in or outside Japan.

2. Design and Development

2.(1) Performance and safety specifications

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

There are no changes in the proposed performance and safety specifications of SUSMED App, and the same specifications are established.

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

Since there is no change in design, and no significant changes in the method of use associated with the change in intended use, PMDA concluded that it is acceptable to establish the same specifications as before.

Performance

Summary of the data submitted

Since there is no change in the design, and no additional tests, etc. were conducted, performance data were not submitted for the present partial change application.

Outline of the review conducted by PMDA

Since there is no change in design, and the method of use is similar to that used previously, PMDA concluded that it is acceptable to omit submission of data.

Safety specifications

Summary of the data submitted

Since there is no change in the design, and no additional tests, etc. were conducted, data on the software development life cycle were not submitted for the present partial change application.

In the review of the application for the initial marketing approval of the SUSMED App, conformity to the specifications related to the usability engineering process was required. However, no data were submitted because the application fell within the transitional measure period during which such requirements were exempted. Conformity to the cybersecurity specifications was also not required for the initial approval, as these requirements were likewise subject to transitional measures. For these reasons, the study result data supporting the product's conformity to specifications for the usability engineering process (JIS T 62366-1:2022) and cybersecurity (JIS T 81001-5-1:2023) were submitted for the present application.

Outline of the review conducted by PMDA

In the partial change application, no changes occurred in the management of software development life cycle arise, and the method of use is similar to that used previously; therefore, PMDA concluded that it is acceptable to omit submission of data on the software development life cycle.

In addition, PMDA concluded that the review of the study result data supporting the product's conformity to the specifications for the usability engineering process and cybersecurity revealed no particular problems.

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

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the SUSMED App to the Essential Principles. Details are shown below.

The conformity of the SUSMED App to Article 1, which stipulates preconditions, etc. for designing medical devices (particularly requirements for users, such as the expected level of technical knowledge and experience of users, and the expected level of education and training to be provided to users):

PMDA's view:

As discussed later in Section "6.B Outline of the review conducted by PMDA," to ensure its efficacy and safety, the SUSMED App should be used based on a thorough understanding of the medical technology related to the product and CBT-I, etc. Accordingly, PMDA decided to attach approval conditions that ensure adherence to the proper use guidelines and implementation of a use-results survey aiming at stepwise cautious introduction of the product.

Based on the above, PMDA comprehensively reviewed the conformity of the SUSMED App to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

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

4.B Outline of the review conducted by PMDA

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

5. Manufacturing Process

5.A Summary of the data submitted

Data on the manufacturing process were not submitted because no changes were made to the manufacturing process for the present application.

5.B Outline of the review conducted by PMDA

PMDA concluded that omission of data on the manufacturing process is acceptable.

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

6.A Summary of the data submitted

In the present application, the results from Study SYK02, which evaluated the effectiveness of therapy using the SUSMED App, were compared with those from Study S02, a clinical study that examined the effects of standard pharmacotherapy in Japan (zolpidem tartrate). Based on an analysis of the results, the efficacy and safety of treatment using the SUSMED App alone were evaluated (hereinafter referred to as the “comparative analysis”).

The data from Study SYK02 were submitted for the review of the initial approval. The aim of Study S02 was to estimate the level of effect of zolpidem tartrate. Table 2 shows an outline of the study plan for both studies.

Table 2. Outline of the plans of Study SYK02 and Study S02

	SYK02	S02
Study title	A clinical study (confirmatory) of non-pharmacotherapy using software Yukumi[i] in patients with insomnia—a sham-controlled multicenter, dynamic allocation, double-blind study	A prospective study that evaluates satisfaction and sleep analysis data for pharmacotherapy in patients with insomnia
Objective	This clinical trial evaluates the efficacy of CBT-I using the SUSMED App at Week 8 in patients with insomnia with a sham app as a control based on the change in AIS as the primary endpoint. Secondary efficacy endpoints are as follows: sleep log (sleep onset latency, sleep efficiency, the number of nocturnal awakenings), CGI-I, necessity of medication at the end of study or treatment discontinuation, item-by-item evaluation of AIS, proportion of patients with an AIS of <6 points For safety endpoints, adverse events and malfunctions are evaluated.	This study evaluates the efficacy of pharmacotherapy in patients with insomnia at Week 8 based on the change in AIS as the primary endpoint. Secondary efficacy endpoints are as follows: sleep log (sleep onset latency, sleep efficiency, the number of nocturnal awakenings), CGI-I, necessity of medication at the end of study or treatment discontinuation, item-by-item evaluation of AIS, proportion of patients with an AIS of <6 points For safety endpoints, adverse events are evaluated.
Type of study	A sham-controlled multicenter, dynamic allocation, parallel-group, double-blind study	A single-arm, multicenter, prospective intervention study
Study population	Patients with insomnia	Same as left
Inclusion criteria	(1) Patients diagnosed with insomnia according to the ICSD-3 who require treatment (2) Patients who have not responded adequately to sleep hygiene education (change in AIS from the time of consent through to enrollment is <5 points) (3) Patients aged ≥20 years at the time of consent (4) Sex: any sex (5) Inpatient or outpatient: outpatient (6) Patients who are capable of understanding the Japanese language used in the SUSMED App (7) Patients who are able to install the SUSMED App, without help, on Android or iOS-based mobile devices on which the app can run, and can use it during the study period (8) Patients who can visit the clinic on the days scheduled for the study (9) Patients who provide written consent to participate in the study	(1) Same as left (2) Same as left (3) Same as left (4) Same as left (5) Same as left (6) — (7) — (8) Same as left (9) Same as left
Exclusion criteria	(1) Patients with an AIS score of <9 points at the time of consent or enrollment (2) Patients with prior treatment with long-acting sleep medications (including antidepressants, anxiolytics) to treat insomnia symptoms (3) Patients who are taking, or have taken within 14 days prior to enrollment, sleep medications to treat insomnia symptoms (including ultrashort-acting, short-acting, and intermediate-acting sleep medications, and over-the-counter sleep aid medications), antidepressants, anxiolytics, herbal medicines	(1) Same as left (2) — (3) Same as left

i This app has all the functions that the SUSMED App has, except for those related to sleep hygiene education.

	SYK02	S02
	(4) Patients whose sleep status between the date of consent (≥7 days before the enrollment) and the enrollment date cannot be obtained from the sleep log, or patients whose sleep status during the above period can be obtained but does not require further improvement (sleep efficiency of ≥85% based on the sleep log; or sleep onset latency of <1 hour)	(4) Same as left
	(5) Patients with psychiatric disorders that are considered to require medication according to the Mini-International Neuropsychiatric Interview (M.I.N.I), or patients with comorbidity of psychiatric disorders being treated with medication (including Alzheimer's disease, Parkinson's disease, and epilepsy)	(5) Same as left
	(6) Patients diagnosed with or suspected of having (according to interview) sleep-related breathing disorders as a comorbidity and who stop breathing during sleep or snore loudly in addition to excessive daytime sleepiness	(6) Same as left
	(7) Patients diagnosed with or suspected of having (according to interview) sleep-related movement disorders (e.g., restless legs syndrome, periodic limb movement disorder) as a comorbidity and who have sleep-related sensations/motor symptoms such as abnormal sensations/movements at night	(7) Same as left
	(8) Patients diagnosed with or suspected of having (according to interview) central hypersomnia (e.g., narcolepsy) as a comorbidity who have excessive daytime sleepiness despite adequate sleep	(8) Same as left
	(9) Patients diagnosed with or suspected of having (according to interview) parasomnia (e.g., rapid eye movement sleep behavior disorder) as a comorbidity and who exhibit abnormal behavior during sleep such as loud vocalization, limb movement, and walking	(9) Same as left
	(10) Patients diagnosed with or suspected of having (according to interview) circadian rhythm disorders (e.g., delayed sleep-phase syndrome) as a comorbidity and who have irregular sleep-wake rhythm such as day night reversal	(10) Same as left
	(11) Patients with a history, or a comorbidity, of alcohol dependence or drug addiction	(11) Same as left
	(12) Patients with cancer, immune disease, or those who have corresponding symptoms of such diseases (including those who were diagnosed or received treatment within the past 5 years)	(12) Same as left
	(13) Pregnant or possibly pregnant or lactating women	(13) Same as left

	SYK02	S02
	(14) Patients who had or are about to undergo major lifestyle changes (e.g., moving, job transfer, change jobs, trip, traveling overseas) within the past 90 days, or during the study participation period	(14) Same as left
	(15) Patients who are or plan to be engaged in night shift work (or whose lifestyle involves day/night reversal of waking/sleeping), work that requires driving vehicles or motorcycles, or are engaged in a dangerous job during the study participation period	(15) Same as left
	(16) Patients who received sleep hygiene education within the preceding 6 months or received cognitive behavioral therapy for insomnia symptoms in the past	(16) —
	(17) Patients who have used the SUSMED App or its prototype apps in clinical trials (Yawn, Yue) in the past	(17) —
	(18) Patients who have used other study drugs or medical devices under development within the preceding 90 days	(18) —
	(19) Patients who are considered to be ineligible by the investigator or subinvestigator	(19) Same as left
Sample size (at the time of analysis)	175 patients (87 of whom are in the active group)	19 patients
Intervention	The study device (app) was downloaded on the patient's smart phone and the app program was used for 56 days.	Zolpidem tartrate 5 mg (Myslee Tablets or its generic drugs) was administered once daily before getting into bed for 8 weeks.
Testing/monitoring items and time frame	Primary efficacy endpoint: change in AIS from baseline to Week 8 Secondary efficacy endpoints: the following items were evaluated (1) Change in AIS item-by-item from baseline to Week 8 (2) Change in the Clinical Global Impressions-Improvement (CGI-I) from baseline to Week 8 (3) Proportion of patients with an AIS of <6 points at Week 8 or treatment discontinuation (4) Necessity of medication at the end of study or treatment discontinuation (5) Change in sleep onset latency, sleep efficiency, and the number of nocturnal awakenings from baseline to the end of treatment based on sleep log (paper-based) and data from actigraph Safety: The following items were evaluated from the time of consent through to the end of study, or to the end of follow-up examination in the event of treatment discontinuation: (1) Adverse events (2) Malfunctions	Primary efficacy endpoint: Same as left Secondary efficacy endpoints: Same as left Safety: The following items were evaluated from the time of consent through to the end of study, or to the end of follow-up examination in the event of treatment discontinuation: (1) Same as left (2) —
Follow-up period	78 days • Screening period: 1 week	Same as left

	SYK02	S02
	• Intervention period: 8 weeks • Follow-up period: 2 weeks	
Concomitant drugs/treatments	(1) Prohibited concomitant medications Use of the following drugs was prohibited from the time of consent through to the end of study or the end of follow-up examination in the event of treatment discontinuation: • Sleep medications (including drugs indicated for insomnia or sleep disorders) • Over-the-counter sleep aid medications • Psychotropic drugs • Antihistamines (excluding second-generation antihistamines) • Herbal medicines (Orengedokuto [Huang Lian Jie Du Tang], Saikokaryukotsuboreito [Chai Hu Jia Long Gu Mu Li Tang], San'oshasinto [San Huang Xie Xin Tang], Kamikihito [Jia Wei Gui Pi Tang], Kamishoyosan [Jia Wei Xiao Yao San], Kihito [Gui Pi Tang], Sansoninto [Suan Zao Ren Tang], Yokukansan [Yi Gan San], Saikokeishikankyoto [Chai Hu Gui Zhi Gan Jiang Tang]) • Sleep-associated supplements • Other drugs considered by the investigator or subinvestigator to affect the efficacy evaluation of insomnia symptoms (2) Restricted concomitant medications Use of the following drugs was restricted from the time of consent through to the end of study or the end of follow-up examination in the event of treatment discontinuation: • Antipyretic analgesics (as-needed use and use of topical medications were allowed if prescribed by a physician. The use of over-the-counter drugs at the patient's discretion was not allowed.) (3) Prohibited concomitant therapies Concomitant therapies considered to affect the efficacy and safety evaluation of the study device (e.g., counseling, psychotherapy, other sleep-related digital app, other sleep hygiene education or other CBT-I) were prohibited from the time of consent through to the end of study or the end of follow-up examination in the event of treatment discontinuation.	(1) Prohibited concomitant medications Use of the following drugs was prohibited from the time of consent through to the end of study or the end of follow-up examination in the event of treatment discontinuation: (Same as left) (2) Restricted concomitant medications Use of the following drugs was restricted from the time of consent through to the end of study or the end of follow-up examination in the event of treatment discontinuation: • Same as left (3) Prohibited concomitant therapies Concomitant therapies considered to affect the efficacy and safety evaluation of the study device (e.g., counseling, psychotherapy, other sleep-related digital app, other sleep hygiene education or other CBT-I) were prohibited from the time of consent through to the end of study or the end of follow-up examination in the event of treatment discontinuation.
Name/number of study sites	(1) [redacted] (2) (3) (4) (5) (6) (7)	(1) Same as left (2) Same as left (3) Same as left (4) Same as left (5) — (6) — (7) —

	SYK02	S02
	(8) [redacted] (9) [redacted] 9 study sites in total	(8) — (9) — 4 study sites in total
Study period[ii]	From [redacted], 20[redacted] to [redacted], 20[redacted]	From [redacted], 20[redacted] to [redacted], 20[redacted]

The results from Study SYK02 were compared with those from Study S02 to evaluate the clinical utility of treatment using the SUSMED App alone. The initial version of the protocol for the comparative analysis study was formulated on [redacted], 20[redacted]. The same efficacy endpoints were assessed in both studies. Results obtained for all endpoints in Study S02 were compared with those from Study SYK02, and the results demonstrated the superiority of the SUSMED App over pharmacotherapy (zolpidem tartrate) in terms of clinical utility. Figure 3 shows the comparative analysis study design and Table 3 summarizes the comparison methods used in this comparative analysis study.

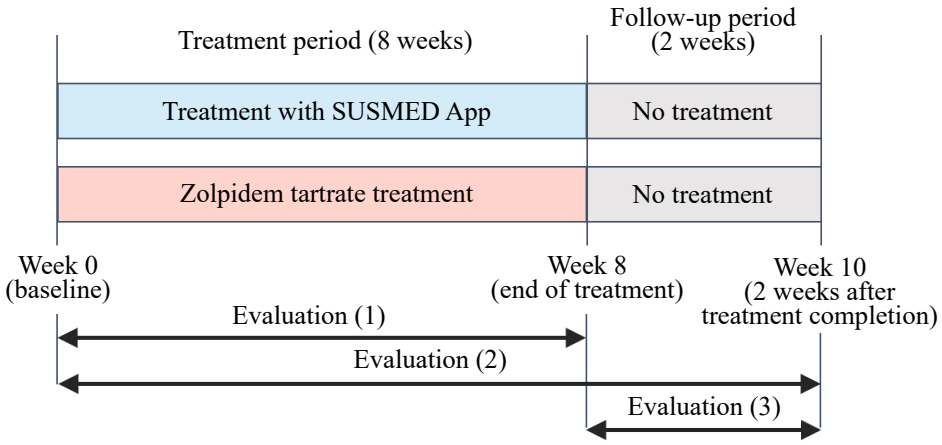

Figure 3. Comparison analysis study design

ii From the day of consent from the first patient to the day of completion of examination/follow-up for the last patient for each study

Table 3. Comparison method used in the comparative analysis study

Analysis population	The same analysis population as that defined in Study SYK02 and Study S02
Endpoints	• Primary endpoint: change in AIS • Secondary endpoint: change in AIS item-by-item • Secondary endpoint: proportion of patients with an AIS of <6 points • Secondary endpoint: assessment by physician (change in Clinical Global Impressions-Improvement [CGI-I]; whether medication is necessary) • Secondary endpoint: change in sleep onset latency, sleep efficiency, and the number of nocturnal awakenings (sleep logs and actigraph data)
Evaluation period	• Evaluation (1): treatment effect at the end of treatment (SUSMED App, zolpidem tartrate) • Evaluation (2): treatment effect in the follow-up period assessed 2 weeks after treatment completion • Evaluation (3): maintenance of treatment effect and remission rate, rebound insomnia after treatment completion

6.A.1) Breakdown of patients

Table 4 shows a breakdown of patients enrolled in this comparative analysis study. In Study SYK02, informed consent was obtained from 221 patients, 175 of whom were enrolled in the study. All patients enrolled used the study device (87 patients in the active group and 88 patients in the sham group). All patients who provided informed consent entered the screening period. After entering the screening period, 46 patients were not enrolled in the study. This was due to the inclusion/exclusion criteria not being met in all 46 cases. All 87 patients who used the SUSMED App completed the 8-week treatment period, and no patients discontinued during the study treatment period. During the follow-up period, 1 patient in the active group discontinued the study at their own request.

In Study S02, informed consent was obtained from 22 patients, 19 of whom were enrolled in the study. All patients enrolled took zolpidem tartrate. All patients who provided informed consent entered the screening period. After entering the screening period, 3 patients were not enrolled in the study. This was due to the inclusion/exclusion criteria not being met (2 patients) and withdrawal of consent for “other reasons” (1 patient). All 19 patients who took zolpidem tartrate completed the 8-week treatment period and the 2-week follow-up period.

In the context of the comparative analysis, the active group in Study SYK02 is referred to as the “App group,” and the group of patients who took zolpidem tartrate in Study S02 is referred to as the “zolpidem tartrate group.”

Table 4. Breakdown of patients

Analysis population: patients enrolled Imputation method: none		
	SUSMED App	Zolpidem tartrate
Number of patients from whom informed consent was obtained	221	22
Number of patients who withdrew at screening	46	3
Reason for withdrawal:		
Inclusion/exclusion criteria not being met	46	2
Other	0	1
Number of patients enrolled	87	19
Number of patients assigned	87	—
Number of patients who completed (treatment period)	87	19
Number of patients who discontinued (treatment period)	0	0
Number of patients who completed (follow-up period)	86	19
Number of patients who discontinued (follow-up period)	1	0
Reasons:		
Withdrawal by patients	1	0
Adverse events	0	0
Malfunctions of device	0	—
Worsening of symptoms, inadequate effectiveness	0	0
Found to be ineligible	0	0
Failure to attend visits due to personal inconvenience	0	0
Other	0	0

6.A.2) Protocol deviations

Table 5 provides details of the deviations from the protocols of Study SYK02 and Study S02. In the App group, 30 protocol deviations occurred in 27 of the 87 patients enrolled. The most common category of deviations other than “other protocol deviations” was “follow-up examinations not implemented or were performed outside the specified time window” (13 deviations).

In the zolpidem tartrate group, 1 protocol deviation occurred in 1 of the 19 patients enrolled, and the case was classified as “violation of method/period of use of device (or taking medication).”

Table 5. Details of protocol deviations

Analysis population: patients enrolled Imputation method: none		
	SUSMED App	Zolpidem tartrate
Number of patients	87	19
Number of patients with protocol deviation	27	1
Protocol deviation categories		
GCP noncompliance	0	—
Disease not covered by study	0	0
Violation of inclusion/exclusion criteria	0	0
Violation of discontinuation criteria	0	0
Violation of method/period of use of device (or taking medication)	0	1
Violation in relation to concomitant drug/therapy	0	0
Follow-up examinations not implemented or were performed outside the specified time window	13	0
Other protocol deviations	17	0

6.A.3) Efficacy analysis population

Table 6 shows the details of the efficacy analysis population in the comparative analysis study. In the App group, 87 patients were included in the mITT[iii] and in the PPS.[iv] In the zolpidem tartrate group, 19 patients were included in the mITT and in the PPS.

Table 6. Details of efficacy analysis population

Analysis population: patients enrolled Imputation method: none		
	SUSMED App	Zolpidem tartrate
Number of patients	87	19
mITT population:		
Patients included	87	19
Patients not included	0	0
PPS population:		
Patients included	87	19
Patients not included	0	0

iii Definition in Study SYK02: of the patients enrolled in the study, those who met the following criteria were excluded: patients who failed to perform reviews every morning and evening; and patients who failed to enter AIS score every 7 days after completion of initial settings.
Definition in Study S02: of the patients enrolled in the study, those who met the following criterion were excluded: patients who failed to perform an AIS assessment.

iv Definition in Study SYK02 and Study S02: of the patients included in the mITT population, those to whom the following apply, which are considered to affect the efficacy evaluation, were excluded: 1) patients not meeting the inclusion/exclusion criteria; 2) patients not meeting the requirements for concomitant drugs/therapies; and 3) patients who did not discontinue treatment despite meeting the requirements for discontinuation.

6.A.4) Patient characteristics

Table 7 shows the patient characteristics in the comparative analysis study.

The mean age was 42.4 years in the App group and 44.1 years in the zolpidem tartrate group; 32 males (36.8%) and 55 females (63.2%) in the App group, and 7 males (36.8%) and 12 females (63.2%) in the zolpidem tartrate group. The mean AIS score at baseline was 13.4 in both groups. There were no marked differences between the groups in the demographic parameters or baseline characteristics.

Table 7. Patient characteristics

Analysis population: mITT population Imputation method: none					
		SUSMED App		Zolpidem tartrate	
Number of patients		87	(proportion)	19	(proportion)
Age	Mean	42.4		44.1	
	Standard deviation	13.5		12.8	
	Minimum	21		22	
	Median	44		47	
	Maximum	72		63	
Age (group)	≥20 years and <40 years	41	47.1%	7	36.8%
	≥40 years and <65 years	40	46.0%	12	63.2%
	≥65 years	6	6.9%	0	0.0%
Sex	Male	32	36.8%	7	36.8%
	Female	55	63.2%	12	63.2%
Have medical history/ comorbidity	Yes	26	29.9%	2	10.5%
	No	61	70.1%	17	89.5%
Prior use of treatment drugs	Used	0	0.0%	0	0.0%
	Not used	87	100.0%	19	100.0%
Use of concomitant drugs	Used	26	29.9%	3	15.8%
	Not used	61	70.1%	16	84.2%
Use of concomitant therapies	Used	0	0.0%	0	0.0%
	Not used	87	100.0%	19	100.0%
Baseline AIS	Mean	13.4		13.4	
	Standard deviation	2.8		2.8	
	Minimum	9		10	
	Median	13		13	
	Maximum	21		21	

6.A.5) Treatment adherence

Table 8 shows the status of treatment adherence in this comparative analysis study. The adherence to medical device use in the App group was 89.3%, and medication adherence in the zolpidem tartrate group was 98.5%.

Table 8. Treatment adherence status

Analysis population: mITT population Imputation method: none		
	SUSMED App	Zolpidem tartrate
Number of patients	87	19
Planned number of device uses	9744	—
Observed number of device uses	8704	—
Device use adherence/medication adherence (%)	89.3	98.5

6.A.6) Efficacy

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

Table 9 shows the change in AIS from baseline at Week 8 (end of treatment) in the mITT population. Change in AIS (mean ± standard deviation) from baseline to Week 8 (end of treatment) was −6.7 ± 4.4 in the App group and −9.9 ± 3.2 in the zolpidem tartrate group, with a between-group difference of 3.2 (P = 0.001), indicating that during the treatment period, the improvement in insomnia symptoms was more significant in the zolpidem tartrate group than in the App group.

Table 9. Change in AIS from baseline to Week 8 (end of treatment) (Evaluation [1])

Analysis population: mITT population Imputation method: none											
		Baseline	Week 8	Change from baseline					Difference from zolpidem tartrate		
Group	N	Mean	Mean	Mean	Min	Median	Max	SD	Difference	P-value[1)]	95% CI
SUSMED App	87	13.4	6.7	−6.7	−19	−7	6	4.4	3.2	0.001	1.5 to 5.0
Zolpidem tartrate	19	13.4	3.5	−9.9	−18	−10	−5	3.2			
1) Welch's t-test											

Table 10 shows change in AIS from baseline to Week 10 (2 weeks after treatment completion) in the mITT population. Change in AIS (mean ± standard deviation) from baseline to Week 10 (2 weeks after treatment completion) was −7.5 ± 4.2 in the App group and −7.9 ± 4.3 in the zolpidem tartrate group, with a between-group difference of 0.4 (P = 0.734), indicating that the improvement in insomnia symptoms in the App group was similar to that in the zolpidem tartrate

group.

Table 10. Change in AIS from baseline to Week 10 (2 weeks after treatment completion) (Evaluation [2])

Analysis population: mITT population Imputation method: none											
		Baseline	Week 10	Change from baseline					Difference from zolpidem tartrate		
Group	N	Mean	Mean	Mean	Min	Median	Max	SD	Difference	*P*-value[1)]	95% CI
SUSMED App	86	13.4	5.9	−7.5	−19	−7	2	4.2	0.4	0.734	−1.9 to 2.6
Zolpidem tartrate	19	13.4	5.5	−7.9	−16	−8	3	4.3			
1) Welch's t-test											

Table 11 shows change in AIS from Week 8 (end of treatment) to Week 10 (2 weeks after treatment completion) in the mITT population. Change in AIS (mean ± standard deviation) from Week 8 (end of treatment) to Week 10 (2 weeks after treatment completion) was −0.8 ± 2.1 in the App group and 2.1 ± 3.7 in the zolpidem tartrate group, with a between-group difference of −2.9 (P = 0.004), indicating that after the completion of treatment, the treatment effect in the App group lasted significantly longer compared to that in the zolpidem tartrate group.

Table 11. Change in AIS from Week 8 (end of treatment) to Week 10 (2 weeks after treatment completion) (Evaluation [3])

Analysis population: mITT population Imputation method: none											
		Week 8	Week 10	Change from Week 8					Difference from zolpidem tartrate		
Group	N	Mean	Mean	Mean	Min	Median	Max	SD	Difference	*P*-value[1)]	95% CI
SUSMED App	86	6.7	5.9	−0.8	−7	0	4	2.1	−2.9	0.004	−4.7 to −1.0
Zolpidem tartrate	19	3.5	5.5	2.1	−2	1	13	3.7			
1) Welch's t-test											

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

Table 12 shows the change in AIS item-by-item from baseline to Week 8 (end of treatment) in the mITT population. The AIS consists of 8 items as shown in Table 12. During the treatment period, the improvement in insomnia symptoms was significantly greater in the zolpidem tartrate group than in the App group for the following items: "awakenings during the night," "overall quality of sleep," "sense of well-being during the day," and "physical and mental functioning capacity during the day." Conversely, the improvement in insomnia symptoms was similar between the groups for the following items: "sleep induction (time required to fall asleep after going to bed)," "awakening earlier than desired and unable to fall back to sleep," "total sleep duration," and

“sleepiness during the day.”

Table 12. Change in AIS item-by-item from baseline to Week 8 (end of treatment) (Evaluation [1])

Analysis population: mITT population
Imputation method: none

			Baseline	Week 8	Change from baseline					Difference from zolpidem tartrate		
	Group	N	Mean	Mean	Mean	Min	Median	Max	SD	Difference	*P*-value[1)]	95% CI
Sleep induction	SUSMED App	87	1.9	0.9	−1.1	−3	−1	1	0.7	0.3	0.130	−0.1 to 0.7
	Zolpidem tartrate	19	1.8	0.4	−1.4	−2	−2	0	0.8			
Awakenings during the night	SUSMED App	87	1.4	0.7	−0.7	−2	−1	1	0.8	0.7	0.002	0.3 to 1.1
	Zolpidem tartrate	19	1.6	0.3	−1.3	−3	−1	0	0.7			
Awakening earlier than desired and unable to fall back to sleep	SUSMED App	87	1.4	0.7	−0.7	−2	−1	2	0.8	0.4	0.086	−0.1 to 0.8
	Zolpidem tartrate	19	1.6	0.6	−1.1	−3	−1	0	0.8			
Total sleep duration	SUSMED App	87	1.8	1.0	−0.8	−2	−1	1	0.7	0.4	0.059	−0.0 to 0.8
	Zolpidem tartrate	19	1.7	0.5	−1.2	−2	−1	0	0.8			
Overall quality of sleep	SUSMED App	87	2.0	1.0	−1.1	−3	−1	0	0.8	0.4	0.033	0.0 to 0.8
	Zolpidem tartrate	19	2.0	0.5	−1.5	−2	−2	0	0.7			
Sense of well-being during the day	SUSMED App	87	1.6	0.8	−0.9	−3	−1	1	0.9	0.5	0.004	0.2 to 0.8
	Zolpidem tartrate	19	1.6	0.3	−1.4	−3	−1	−1	0.6			
Physical and mental functioning capacity during the day	SUSMED App	87	1.4	0.7	−0.7	−3	−1	2	0.8	0.7	0.001	0.3 to 1.1
	Zolpidem tartrate	19	1.6	0.2	−1.4	−3	−1	0	0.7			
Sleepiness during the day	SUSMED App	87	1.8	0.9	−0.8	−3	−1	1	0.7	0.0	0.732	−0.3 to 0.2
	Zolpidem tartrate	19	1.4	0.6	−0.8	−2	−1	0	0.5			

1) Welch’s t-test

Table 13 shows change in AIS item-by-item from baseline to Week 10 (2 weeks after treatment completion) in the mITT population. For all 8 items, the improvement in insomnia symptoms in the App group was similar to that of the zolpidem tartrate group.

Table 13. Changes in AIS item-by-item from baseline to Week 10 (2 weeks after treatment completion) (Evaluation [2])

Analysis population: mITT population Imputation method: none												
			Baseline	Week 10	Change from baseline					Difference from zolpidem tartrate		
	Group	N	Mean	Mean	Mean	Min	Median	Max	SD	Difference	*P*-value[1)]	95% CI
Sleep induction	SUSMED App	86	1.9	0.9	−1.1	−3	−1	1	0.7	−0.2	0.389	−0.5 to 0.2
	Zolpidem tartrate	19	1.8	0.9	−0.9	−2	−1	1	0.7			
Awakenings during the night	SUSMED App	86	1.4	0.5	−0.8	−2	−1	1	0.8	0.2	0.437	−0.3 to 0.6
	Zolpidem tartrate	19	1.6	0.6	−1.0	−3	−1	0	0.8			
Awakening earlier than desired and unable to fall back to sleep	SUSMED App	86	1.4	0.7	−0.7	−2	−1	1	0.8	0.2	0.201	−0.1 to 0.5
	Zolpidem tartrate	19	1.6	0.7	−0.9	−2	−1	0	0.6			
Total sleep duration	SUSMED App	86	1.8	0.9	−0.9	−2	−1	1	0.8	0.0	0.998	−0.5 to 0.5
	Zolpidem tartrate	19	1.7	0.8	−0.9	−3	−1	1	1.0			
Overall quality of sleep	SUSMED App	86	2.0	0.8	−1.2	−3	−1	0	0.7	−0.1	0.501	−0.5 to 0.3
	Zolpidem tartrate	19	2.0	0.9	−1.1	−2	−1	0	0.7			
Sense of well-being during the day	SUSMED App	86	1.6	0.7	−1.0	−3	−1	1	0.9	0.2	0.227	−0.2 to 0.6
	Zolpidem tartrate	19	1.6	0.4	−1.2	−3	−1	0	0.7			
Physical and mental functioning capacity during the day	SUSMED App	86	1.4	0.5	−0.9	−3	−1	1	0.8	0.3	0.249	−0.2 to 0.7
	Zolpidem tartrate	19	1.6	0.4	−1.2	−2	−1	1	0.9			
Sleepiness during the day	SUSMED App	86	1.8	0.9	−0.8	−3	−1	0	0.7	−0.2	0.22	−0.6 to 0.1
	Zolpidem tartrate	19	1.4	0.8	−0.6	−2	−1	1	0.7			
1) Welch's t-test												

Table 14 shows changes in AIS item-by-item from Week 8 (end of treatment) to Week 10 (2 weeks after treatment completion) in the mITT population. After completion of treatment, treatment effect in the App group lasted significantly longer compared to that in the zolpidem tartrate group for the following items: "sleep induction (time required to fall asleep after going to bed)," "awakenings during the night," "total sleep duration," "overall quality of sleep," "sense of well-being during the day," and "physical and mental functioning capacity during the day." Improvements in "awakening earlier than desired and unable to fall back to sleep" and "sleepiness

during the day" tended to be greater in the App group than in the zolpidem tartrate group after the completion of treatment.

Table 14 Change in AIS item-by-item from Week 8 (end of treatment) to Week 10 (2 weeks after treatment completion) (Evaluation [3])

Analysis population: mITT population Imputation method: none												
			Week 8	Week 10	Change from baseline					Difference from zolpidem tartrate		
	Group	N	Mean	Mean	Mean	Min	Median	Max	SD	Difference	*P*-value[1)]	95% CI
Sleep induction	SUSMED App	86	0.9	0.9	0.0	−1	0	1	0.4	−0.5	0.009	−0.8 to −0.1
	Zolpidem tartrate	19	0.4	0.9	0.5	−1	0	2	0.7			
Awakenings during the night	SUSMED App	86	0.7	0.5	−0.2	−1	0	1	0.4	−0.5	0.000	−0.7 to −0.2
	Zolpidem tartrate	19	0.3	0.6	0.3	0	0	1	0.5			
Awakening earlier than desired and unable to fall back to sleep	SUSMED App	86	0.7	0.7	0.0	−2	0	1	0.6	−0.2	0.298	−0.4 to 0.1
	Zolpidem tartrate	19	0.6	0.7	0.1	−1	0	1	0.6			
Total sleep duration	SUSMED App	86	1.0	0.9	−0.1	−2	0	1	0.5	−0.4	0.044	−0.7 to −0.0
	Zolpidem tartrate	19	0.5	0.8	0.3	−1	0	2	0.7			
Overall quality of sleep	SUSMED App	86	1.0	0.8	−0.2	−1	0	1	0.5	−0.5	0.016	−0.9 to −0.1
	Zolpidem tartrate	19	0.5	0.9	0.4	−1	0	2	0.8			
Sense of well-being during the day	SUSMED App	86	0.8	0.7	−0.1	−2	0	1	0.5	−0.3	0.048	−0.5 to −0.0
	Zolpidem tartrate	19	0.3	0.4	0.2	−1	0	1	0.5			
Physical and mental functioning capacity during the day	SUSMED App	86	0.7	0.5	−0.2	−2	0	1	0.6	−0.4	0.009	−0.8 to −0.1
	Zolpidem tartrate	19	0.2	0.4	0.2	−1	0	2	0.6			
Sleepiness during the day	SUSMED App	86	0.9	0.9	0.0	−1	0	1	0.5	−0.2	0.226	−0.4 to 0.1
	Zolpidem tartrate	19	0.6	0.8	0.2	0	0	2	0.5			
1) Welch's t-test												

Table 15 shows the proportion of patients with an AIS of <6 points at Week 8 (end of treatment) in the mITT population. The proportion of patients (mean) with an AIS score of <6 points at Week

8 (end of treatment) was 37.9% in the App group and 73.7% in the zolpidem tartrate group, with a between-group difference of −35.8% (P = 0.004), indicating that during the treatment period, the improvement in insomnia symptoms in the zolpidem tartrate group was significantly greater than in the App group.

Table 15. Proportion of patients with an AIS of <6 points at Week 8 (end of treatment) (Evaluation [1])

Analysis population: mITT population
Imputation method: none

		Patients with AIS <6 points		Difference from zolpidem tartrate		
Group	N	n	Proportion (%)	Difference (%)	*P*-value[1)]	95% CI
SUSMED App	87	33	37.9	−35.8	0.004	−58.0% to −13.5%
Zolpidem tartrate	19	14	73.7			

1) Testing of difference in population proportions

Table 16 shows the proportion of patients with an AIS of <6 points at Week 10 (2 weeks after treatment completion) in the mITT population. The proportion (mean) of patients with an AIS of <6 points at Week 10 (2 weeks after treatment completion) was 48.8% in the App group and 57.9% in the zolpidem tartrate group, with a between-group difference of −9.1% (P = 0.475), indicating that the improvement in insomnia symptoms in the App group was similar to that in the zolpidem tartrate group.

Table 16. Proportion of patients with an AIS of <6 points at Week 10 (2 weeks after treatment completion) (Evaluation [2])

Analysis population: mITT population
Imputation method: none

		Patients with AIS <6 points		Difference from zolpidem tartrate		
Group	N	n	Proportion (%)	Difference (%)	*P*-value[1)]	95% CI
SUSMED App	86	42	48.8	−9.1	0.475	−33.6% to 15.5%
Zolpidem tartrate	19	11	57.9			

1) Testing of difference in population proportions

Table 17 shows the proportion of patients with an AIS of <6 points at Week 8 (end of treatment) and Week 10 (2 weeks after treatment completion) in the mITT population. The proportion (mean)

of patients with an AIS of <6 points increased by 10.9 percentage points, from 37.9% to 48.8% in the App group while the proportion decreased by 15.8 percentage points, from 73.7% to 57.9% in the zolpidem tartrate group. After treatment, the improvement in insomnia symptoms was sustained in the App group, while insomnia symptoms worsened in the zolpidem tartrate group, suggesting that rebound insomnia occurred following discontinuation of the sleep medication. The treatment effect lasted longer and remission rate increased after the completion of treatment in the App group compared with the zolpidem tartrate group.

Table 17. Proportion of patients with an AIS of <6 points at Week 8 (end of treatment) and Week 10 (2 weeks after treatment completion) (Evaluation [3])

Analysis population: mITT population Imputation method: none						
		Week 8			Week 10	
Group	N	n	Proportion (%)	N	n	Proportion (%)
SUSMED App	87	33	37.9%	86	42	48.8%
Zolpidem tartrate	19	14	73.7%	19	11	57.9%

Table 18 shows the change from baseline to Week 8 (end of treatment) in CGI-I, a physician assessment of improvement/worsening in the mITT population. Change in CGI-I (mean ± standard deviation) from baseline to Week 8 (end of treatment) was 1.3±0.8 in the App group and 2.1±0.8 in the zolpidem tartrate group, with a between-group difference of −0.8 (P = 0.001), indicating that during the treatment period, the improvement in insomnia symptoms in the zolpidem tartrate group was significantly greater than that in the App group.

Table 18. Change in CGI-I from baseline to Week 8 (end of treatment) (Evaluation [1])

Analysis population: mITT population Imputation method: none											
		Baseline	Week 8	Change from baseline					Difference from zolpidem tartrate		
Group	N	Mean	Mean	Mean	Min	Median	Max	SD	Difference	P-value[1)]	95% CI
SUSMED App	87	4	5.3	1.3	0	1	3	0.8	−0.8	0.001	−1.2 to −0.4
Zolpidem tartrate	19	4	6.1	2.1	0	2	3	0.8			
1) Welch's t-test											

Table 19 shows the proportion of patients in the mITT population for whom medication was needed as assessed by the physician at Week 10 (2 weeks after treatment completion). The proportion of patients for whom medication was deemed necessary based on whether the treatment effect was maintained and the patient was in remission at the evaluation timepoint was

7.0% (6 patients) in the App group and 26.3% (5 patients) in the zolpidem tartrate group, with a between-group difference of −19.3% (P = 0.013). This indicates that, based on the physician's assessment, maintenance of the treatment effect and remission rates were significantly better in the App group than in the zolpidem tartrate group after the completion of treatment.

Table 19. Necessity of medications at Week 10 (2 weeks after treatment completion) (Evaluation [2])

Analysis population: mITT population Imputation method: none								
		Unnecessary		Necessary		Difference from zolpidem tartrate		
Group	N	n	Proportion (%)	n	Proportion (%)	Difference	*P*-value[1)]	95% CI
SUSMED App	86	80	93.0	6	7.0	−19.3	0.013	−39.9% to 1.2%
Zolpidem tartrate	19	14	73.7	5	26.3			
1) Testing of difference in population proportions								

Changes from baseline in sleep onset latency, sleep efficiency, and the number of nocturnal awakenings in the mITT population based on sleep logs and actigraph data are shown in Table 20 and Table 21, respectively. Both sleep log and actigraph data indicate no significant differences between the App group and the zolpidem tartrate group in terms of the effect on improvement in insomnia symptoms after the completion of treatment.

Table 20. Change from baseline in sleep onset latency, sleep efficiency, and the number of nocturnal awakenings (sleep logs)

Analysis population: mITT population Imputation method: none											
		Baseline	End	Change from baseline					Difference from zolpidem tartrate		
Group	N	Mean	Mean	Mean	Min	Median	Max	SD	Difference	*P*-value[1)]	95% CI
Sleep onset latency (min)											
SUSMED App	86	94.6	56.2	−38.4	−154.3	−34.3	64.3	36.3	−10.1	0.081	−21.6 to 1.3
Zolpidem tartrate	19	78.4	50.1	−28.3	−64.3	−30	8.6	18.2			
Sleep efficiency (%)											
SUSMED App	86	69.7	80.2	10.4	−35.3	11.5	34.6	9.8	0.4	0.821	−3.0 to 3.8
Zolpidem tartrate	19	72.6	82.6	10.1	−1.9	10.3	25.2	5.8			
Number of nocturnal awakenings (times)											
SUSMED App	86	1.3	1.0	−0.3	−2.0	−0.3	2.7	0.7	0.2	0.416	−0.3 to 0.7
Zolpidem tartrate	19	1.7	1.2	−0.5	−2.3	−0.6	2	0.9			
1) Welch's t-test											

Table 21. Change from baseline in sleep onset latency, sleep efficiency, and the number of nocturnal awakenings (actigraph data)

Analysis population: mITT population
Imputation method: none

		Baseline	End	Change from baseline					Difference from zolpidem tartrate		
Group	N	Mean	Mean	Mean	Min	Median	Max	SD	Difference	*P*-value[1)]	95% CI
Sleep onset latency (min)											
SUSMED App	73	92.9	65.0	-27.9	-98.7	-27.0	34.1	30.1	-12.3	0.057	-24.9 to 0.4
Zolpidem tartrate	16	70.0	54.4	-15.6	-46.7	-10.9	24.6	20.4			
Sleep efficiency (%)											
SUSMED App	73	69.3	75.9	6.6	-14.5	6.7	23.1	8.0	2.0	0.128	0.6 to 4.6
Zolpidem tartrate	16	75.1	79.7	4.6	-5.6	4.7	10.8	3.6			
Number of nocturnal awakenings (times)											
SUSMED App	73	23.6	23.6	0.0	-15.1	-0.1	12.0	6.5	2.7	0.122	-0.8 to 6.3
Zolpidem tartrate	16	25.7	23.0	-2.7	-14.2	-2.9	13.0	6.1			

1) Welch's t-test

6.A.7) Safety

In Study SYK02, no adverse reactions or malfunctions associated with the SUSMED App were reported, and the results revealed no safety concerns that may cause problems.

In Study S02, although adverse events occurred in 2 of 19 patients (10.5%), there were no adverse events for which a causal relationship to the study drug could not be ruled out. No adverse events led to treatment discontinuation or death. There were no serious adverse events or severe adverse events. Reported adverse events were mild in severity.

Zolpidem tartrate[v] was launched in December 2000. The incidence of adverse reactions associated with zolpidem tartrate was 16.5% (13 of 79 patients) in the Japanese phase III double-blind study (control, nitrazepam), 9.7% (7 of 72 patients) in the Japanese phase III double-blind study (control, triazolam), and 31.3% (66 of 211 patients) in the Japanese phase III double-blind study (equivalence study; control, zopiclone). Dayvigo Tablets[vi] (lemborexant), a sleep medication with a new mechanism of action, was launched in July 2020. The incidence of adverse reactions associated with lemborexant was 28.2% (249 of 884 patients) in the phase III clinical study (Study 303, a global study).

v Myslee Tablets 5 mg (approval No. 21200AMZ00560), Myslee Tablets 10 mg (approval No. 21200AMZ00561)
vi Dayvigo Tablets 2.5 mg (approval No. 30200AMX00017000), Dayvigo Tablets 5 mg (approval No. 30200AMX00018000), Dayvigo Tablets 10 mg (approval No. 30200AMX00019000)

6.B Outline of the review conducted by PMDA

PMDA's review focused on the following points:

(1) Submitted comparative studies

(2) Efficacy of SUSMED App

(3) Clinical positioning

6.B.(1) Submitted comparative studies

6.B.(1).1) Comparability of the submitted studies

In the present application, applicant submitted an analysis comparing the results from the 2 studies conducted separately (Studies SYK02 and S02) as data for evaluating the efficacy and safety of the SUSMED App in providing support for the treatment of insomnia. The applicant explained the reason why it considered that the SUSMED App can be evaluated adequately without conducting a prospective, controlled comparative study as follows.

The objective of comparing data from the studies in the comparative analysis was to determine if the treatment effect of the SUSMED App persists after treatment completion and whether remission rates improve, in contrast to zolpidem tartrate, which has been shown to cause rebound insomnia after the end of treatment. The comparative analysis is considered appropriate because, after ensuring the quality of the data from both Study SYK02 and Study S02, it was possible to determine whether the efficacy and safety of the SUSMED App and zolpidem tartrate were evaluated in substantially identical patient populations in terms of the "study protocols," "implementation system/implementation status," and "results." The following sections discuss the comparability of the studies from the standpoints of "study protocols," "implementation system/implementation status," and "results."

6.B.(1).1).(a) Study protocols

i) Study population

Because Study S02 was a study using a sleep medication, inclusion criteria related to the patient's ability to use the SUSMED App were unnecessary; therefore, in Study S02, inclusion criteria (6) and (7) (Table 2) established in Study SYK02 were removed. In clinical practice in Japan, patients who received prior treatment with long-acting sleep medications differ from those taking short-acting sleep medications such as zolpidem tartrate; i.e., they represent patients in a later phase of insomnia treatment. Given these circumstances, it was considered that patients meeting exclusion criterion (2) from Study SYK02 would naturally be excluded from Study S02 without the need to specify exclusion criterion (2); therefore, it was decided that exclusion criterion (2) was unnecessary. Furthermore, since Study S02 is a pharmacotherapy-based intervention study, it is not necessary to take into account the factors considered to directly affect efficacy in Study

SYK02, i.e., sleep hygiene education, cognitive behavior therapy, and the patient's use of the SUSMED App; therefore, exclusion criteria (16), (17), and (18) of Study SYK02 were removed.

The baseline characteristics of the enrolled patients are shown in Table 7. No marked differences were observed between the groups in terms of the demographic parameters or baseline characteristics. Therefore, based on the inclusion/exclusion criteria for Studies SYK02 and S02, it is possible to conclude that the patient populations enrolled in both studies were essentially the same.

ii) Evaluation method

In Study S02, the endpoint on malfunctions, one of the safety endpoints in Study SYK02, was removed, and only adverse event data were collected.

iii) Study sites/number of study sites

All 4 study sites at which Study S02 was conducted were also sites where Study SYK02 was conducted. Therefore, there were no differences in terms of the level of understanding of the protocols for both studies, or in the criteria used to evaluate efficacy and safety.

iv) Sample size

Study SYK02 was designed to assess the efficacy of the SUSMED App compared with the sham app. The sample size for Study S02 was determined to provide a basis for interpreting the efficacy results of the SUSMED App obtained in Study SYK02. Because the sample sizes for Study SYK02 and Study S02 were calculated independently, differences in sample sizes were the result.

Even if sample sizes differ, statistical hypothesis testing is generally valid. The analysis adopted a test for difference between unpaired means (Welch's t-test), in which the effect of sample size difference (bias) is taken into account in the evaluation. In Welch's t-test, the larger the sample size in either group, the larger the test statistic t becomes and the smaller the *P*-value becomes, making it easier to detect statistically significant differences. Conversely, smaller sample sizes reduce the test statistic t and increase the *P*-value, making it harder to detect statistical differences.

Although there was a sample size imbalance (bias) between the App group (N = 87) and the zolpidem tartrate group (N = 19), the comparative analysis was conducted using Welch's t-test, which takes the effect of the imbalanced sample size (bias) into account. Therefore, the difference in sample size will not necessarily lead to an analysis result biased in favor of the SUSMED App.

6.B.(1).1).(b) Implementation system/implementation status

i) Implementation system

A document-based inspection and a data integrity assessment were performed for Study SYK02 at the time of the initial approval, and it was concluded that there were no obstacles to conducting the review for marketing approval.

Study S02 was [redacted].

Based on the above, from the perspective of the implementation system for the study, it was concluded that conducting a comparison of data from Studies SYK02 and S02 was appropriate.

ii) Implementation status

In [redacted] 20[redacted], the Institutional Review Board (IRB) approved the implementation of Study SYK02 at a total of 9 study sites. In [redacted] of the same year, the data were unblinded and the data set for the analysis was obtained. The conduct of Study S02 at 4 study sites was approved at [redacted] in [redacted] 20[redacted], and the data set for the analysis was obtained in [redacted] 20[redacted]. Thus, the sites for Study S02 had already been selected and the study had started before the results of Study SYK02 became available, and it was impossible to intentionally select specific study sites for Study S02 based on the results of Study SYK02.

To verify any possible biases in efficacy interpretation in favor of the SUSMED App caused by study sites selected, the results in the mITT population from baseline to Week 8 (end of treatment), from baseline to Week 10 (2 weeks after treatment completion), from Week 8 (end of treatment) to Week 10 (2 weeks after treatment completion) were reviewed. Table 22 shows a comparison of the change in AIS between all 9 SYK02 study sites and the 4 SYK02 study sites selected for Study S02 from among the 9 study sites. In all evaluation periods, the AIS changes at the 4 SYK02 study sites selected for Study S02 were comparable to the AIS changes at all 9 study sites. Therefore, it was concluded that the results for the 4 S02 study sites can reasonably be interpreted as the representative of the overall results for Study SYK02.

Accordingly, based also on the implementation status it was considered reasonable to compare the study results of SYK02 and S02.

Table 22. Comparison of AIS changes among all the SYK02 study sites and the 4 SYK02 study sites selected for Study S02

Analysis population: mITT population
Imputation method: none

		From baseline to Week 8 (end of treatment)				From baseline to Week 10 (2 weeks after treatment completion)				From Week 8 to Week 10			
	Group	N	Baseline mean	Week 8 mean	Change from baseline	N	Baseline mean	Week 10 mean	Change from baseline	N	Week 8 mean	Week 10 mean	Change from Week 8
Study SYK02	SUSMED App	87	13.4	6.7	−6.7	86	13.4	5.9	−7.5	86	6.7	5.9	−0.8
4 study sites of Study SYK02 selected for Study S02	SUSMED App	42	13.1	6.7	−6.4	41	13.1	6.0	−7.2	41	6.7	6.0	−0.8

6.B.(1).1).(c) Results

Data on disposition of patients (Table 4) show that only 1 patient in the App group discontinued[vii] the study during the follow-up period among those enrolled in Study SYK02. In Study S02, all patients enrolled completed the follow-up period.

Data on protocol deviations (Table 5) show that a total of 30 deviations occurred in 27 of the 87 patients in the App group enrolled in the study. The most common deviation category except for "other protocol deviations" was "follow-up examinations not implemented or were performed outside the specified time window" (13 deviations). In the zolpidem tartrate group, 1 protocol deviation occurred in 1 of the 19 patients enrolled, and this case was "violation of method/period of use of device."

Data on treatment adherence status (Table 8) show that the treatment was implemented in 89.3% of patients in the App group, while the medication adherence in the zolpidem tartrate group was 98.5%. It is known that in clinical practice, sleep medication compliance is low in Japan. The Japanese Clinical Guidelines state that "medication adherence in Japanese patients is low, which is attributed to the fact that many Japanese have concerns/anxiety about taking sleep medication." In contrast, adherence in Study S02 was high, and the results are considered to exceed what can generally be expected in clinical practice.

In a study,[6] in which zolpidem tartrate 5 to 10 mg was administered for 2 weeks in addition to treatment intervention for nocturia, the change in AIS from baseline to Week 2 was −6.1 (12.9 at baseline and 6.8 at Week 2). The Review Report of Dayvigo Tablets[7] states that in a foreign phase III study, following administration of zolpidem tartrate extended-release tablets (unapproved drug

vii The reason for discontinuation was "withdrawal by patient."

in Japan) 6.25 mg for 30 days, the change in sleep onset latency (based on the sleep log) from baseline to the end of treatment was −16.9 (60.54 at baseline and 43.64 after treatment). In Study S02, as shown in Table 23, the change in AIS from baseline was −8.5 at Week 4 and −9.9 at Week 8 (13.4 at baseline, 4.9 at Week 4, and 3.5 at Week 8). As shown in Table 20, the change in sleep onset latency (based on the sleep log) was −28.3 (78.4 at baseline and 50.1 after treatment). These results indicate that the results from Study S02 are comparable to those from the above-mentioned studies.

Table 23. Change in AIS over time

Analysis population: mITT population Imputation method: none							
Timepoint	Group	N	Mean	Min	Median	Max	SD
Baseline	SUSMED App	87	13.4	9	13	21	2.8
	Zolpidem tartrate	19	13.4	10	13	21	2.8
Week 1	SUSMED App	87	9.9	1	10	21	3.8
	Zolpidem tartrate	—	—	—	—	—	—
Week 2	SUSMED App	87	9.6	0	9	21	3.8
	Zolpidem tartrate	—	—	—	—	—	—
Week 3	SUSMED App	87	9.0	0	8	22	4.4
	Zolpidem tartrate	—	—	—	—	—	—
Week 4	SUSMED App	87	8.4	0	8	23	4.2
	Zolpidem tartrate	19	4.9	0	4	14	3.9
Week 5	SUSMED App	87	7.8	0	8	22	4.2
	Zolpidem tartrate	—	—	—	—	—	—
Week 6	SUSMED App	87	7.6	0	8	22	4.5
	Zolpidem tartrate	—	—	—	—	—	—
Week 7	SUSMED App	87	7.0	0	8	20	4.2
	Zolpidem tartrate	—	—	—	—	—	—
Week 8	SUSMED App	87	6.7	0	7	22	4.5
	Zolpidem tartrate	19	3.5	0	3	10	3.1
Week 10	SUSMED App	86	5.9	0	6	22	4.0
	Zolpidem tartrate	19	5.5	1	5	13	3.5

Based on the above, although Study S02 was a single-arm study of zolpidem tartrate, the status of adherence and results obtained in Study S02 do not show a bias in favor of the SUSMED App when the results from Studies S02 and SYK02 are compared.

As shown in Table 7, the data on patient characteristics do not show any marked differences in terms of demographic parameters and baseline characteristics; however, there are some differences between the groups including non-enrollment of patients ≥65 years in Study S02.

Accordingly, age, sex, and baseline values were used as covariates, and adjustments were made using inverse probability of treatment weighting (IPTW) based on propensity scores to assess the robustness of the comparative analysis. Table 24 shows a comparison of adjusted results for Studies SYK02 and S02. There was no change in the interpretation of results after adjustment; therefore, it is considered that the difference in the patient characteristics between Studies SYK02 and S02 did not affect the results of comparison.

Table 24. Comparison of results for Studies SYK02 and S02 adjusted by IPTW

Analysis population: mITT
Adjustment method: inverse probability of treatment weighting (IPTW) based on propensity score

			Adjustment by IPTW		
			Result for SUSMED App difference from zolpidem tartrate		
			Coefficient (continuous) or odds ratio (binary)	*P*-value[1)]	95% CI[2)]
Continuous outcomes	Change in AIS	From baseline to Week 8 (end of treatment)	3.2	0.000	1.7 to 4.8
		From baseline to Week 10 (2 weeks after treatment completion)	0.4	0.646	-1.3 to 2.1
		From Week 8 (end of treatment) to Week 10 (2 weeks after treatment completion)	-2.8	0.000	-4.4 to -1.3
	Change in Clinical Global Impressions-Improvement (CGI-I)	From baseline to Week 8 (end of treatment)	-0.8	0.000	-1.1 to -0.4
Binary outcomes	Proportion of patients with AIS <6 points	Week 8 (end of treatment)	-1.5	0.002	-2.5 to -0.6
		Week 10 (2 weeks after treatment completion)	-0.4	0.382	-1.3 to 0.5
	Necessity of medication	Week 10 (2 weeks after treatment completion)	-1.5	0.022	-2.8 to -0.2

1) *P*-value in multiple regression (continuous), *P*-value in logistic regression (binary)
2) CI using robust variance

6.B.(1).2) Limitations in the evaluation of the comparative analysis

PMDA asked the applicant to explain the appropriateness of the method and the limitations of its evaluation of the efficacy and safety of the SUSMED App using Study S02 as an external control.

The applicant's explanation:

Based on the "Points to consider for externally controlled trials (Early consideration)" issued by PMDA on March 24, 2025, the appropriateness and the limitations of the comparative analysis are discussed in the following sections in terms of considerations in trial planning (study population; treatment; timing of data collection; index date and observation period; endpoints; intercurrent events; number of participants/patients [sample size]) and considerations for statistical analysis (pre-specification of the statistical analysis plan; statistical methods used in externally controlled trials; addressing limitations of data and comparisons).

6.B.(1).2).(a) Considerations in trial planning

i) Study population

It can be concluded that the study populations of Study SYK02 (SUSMED App) and S02 (zolpidem tartrate) were substantially identical based on the study protocols, implementation system/implementation status, and results, allowing for evaluation of the efficacy and safety of the SUSMED App and zolpidem tartrate in comparable populations.

In particular, potential confounding factors that could have affected the estimation of treatment effects include the allocation factors in Study SYK02, namely AIS scores and study sites. However, the analysis of demographic parameters and baseline characteristics showed that there was no imbalance between the App and zolpidem tartrate groups in the distribution of AIS scores. Study sites were aligned because Study S02 was conducted at 4 of the 9 study sites at which Study SYK02 was conducted. Additionally, medical history/comorbidity, treatment drugs, concomitant drugs/therapies were examined as possible confounding factors that may have affected the estimation of treatment effects. In the protocols of both studies, exclusion criteria were established to exclude patients with psychiatric disorders and patients with non-insomnia sleep-related disorders such as sleep apnea to eliminate the effects of such confounding factors. The results for demographic parameters and baseline characteristics revealed no imbalanced distributions between the groups.

In comparative analyses between the data from all 9 SYK02 study sites and the Study S02 data, as well as between the SYK02 study data from the 4 study sites that also conducted Study S02 and the Study S02 data, no adjustments for confounding factors were made. There are some differences, for instance, patients aged ≥65 years were not enrolled in Study S02. Accordingly, the results were adjusted by IPTW based on propensity score with age, sex, and baseline as covariates, and the results confirmed the robustness of the comparative analysis results.

As shown above, possible confounding factors that may have affected the estimation of treatment effect were examined for study protocol formulation before the implementation of studies. Consequently, demographic parameters and baseline characteristics revealed no imbalanced distributions between the groups. However, if unmeasured confounding factors exist that could influence the estimation of therapeutic effects, they cannot be adjusted for since this is not a randomized clinical trial (RCT). This represents a limitation of using external controls for comparative evaluation.

ii) Treatment

In Study S02, patients were treated with 5 mg of zolpidem tartrate, once daily before bedtime for 8 weeks as per clinical practice, i.e., the same duration as in Study SYK02. Treatment adherence was 98.5% (89.3% in the App group in Study SYK02). No use of prohibited concomitant drugs/therapies (the same as those in Study SYK02) were reported in Study S02. Because of equivalence in study protocols and implementation system between Studies SYK02 and S02, both conducted as trial or research but not as routine clinical practice, there were no essential differences in medical care provided owing to environmental differences.

Based on the above, the studies were conducted according to the protocols developed with the potential between-group imbalance taken into account, and possible impact of any potential between-group imbalance on the interpretation of results is thus considered acceptable within the scope of the protocol. At the same time, unlike in an RCT, when there is a possibility that any unmeasured between-group imbalance affects the interpretation of results, this possibility cannot be taken into account. This is considered a limitation of comparative evaluation employing external controls.

iii) Timing of data collection

In [redacted] 20[redacted], conducting Study SYK02 at a total of 9 study sites was approved by the IRB. In [redacted] of the same year, data were unblinded and the dataset was obtained for analyses. Conducting Study S02 at a total of 4 study sites was approved at [redacted] in [redacted] 20[redacted], and the dataset was obtained for analyses in [redacted] of the following year.

Study S02 began before the unblinding of Study SYK02 and ended within the same time period, and there were no effects on comparability regarding data collection timing.

iv) Index date and observation period

The index date was defined as the enrollment date (treatment initiation date) for both Studies SYK02 and S02, and there were no reports of deviations from the study protocols. In the study protocols, the observation period was divided into a screening period (1 week), an intervention period (8 weeks), and a follow-up period (2 weeks), and this schedule was identical in both studies.

v) Endpoints

In both Studies SYK02 and S02, sleep hygiene education was implemented during the 1-week screening period before the start of treatment, and the inclusion criterion “patients who have not responded adequately to sleep hygiene education (change in AIS from the time of consent through to enrollment is <5 points)” was established. Psychological effects that patients may experience when participating in a clinical study, instead of receiving routine medical care, and those that

may develop early after the start of treatment have been minimized. Table 25 shows change from baseline in objective sleep onset latency reported in the Review Report of Dayvigo Tablets: data from a global phase III placebo-controlled RCT (medication was taken for 6 months from the start of the study under double-blind conditions, followed by a 6-month open-label phase) and a foreign phase III study (medication was taken for 30 days under double-blind conditions); data from Studies SYK02 and S02 based on sleep logs, etc. In the combined data from the 2 phase III studies of Dayvigo Tablets (under double-blind conditions), the change from baseline in sleep onset latency was −8.3 to −17.6 for placebo, −17.8 to −27.3 for Dayvigo Tablets 5 mg, −20.2 to −26.4 for Dayvigo Tablets 10 mg, and −16.9 for zolpidem tartrate 6.25 mg. In Study SYK02, the change from baseline in sleep onset latency in the App group was −38.4. While it is difficult to rule out psychological effects such as placebo effect, the result for the SUSMED App shows greater changes compared to those in all treatment groups in the 2 phase III studies of Dayvigo Tablets, and it is considered that on the whole, the efficacy of the SUSMED App was demonstrated. Furthermore, the change from baseline in sleep onset latency at Month 3 and Month 6 in the Dayvigo Tablets 5 mg and 10 mg groups in the global phase III study during the double-blind period was maintained in the following 6-month open-label period. These findings suggest that the effect observed under blinded conditions remained almost unchanged in the subsequent open-label period, which may indicate a small psychological effect (e.g., placebo effect); therefore, it is considered possible to perform the comparative evaluation.

Table 25. Change from baseline in subjective sleep onset latency based on sleep logs, etc.

(minutes)

	SYK02	S02	Global phase III			Foreign phase III (*3)			
	SUSMED App	Zolpidem tartrate 5 mg	Placebo (*1)	Dayvigo 5 mg (*2)	Dayvigo 10 mg(*2)	Placebo	Dayvigo 5 mg	Dayvigo 10 mg	Zolpidem tartrate ER 6.25 mg
Month 1	—	—	—	−17.8	−20.2	−8.3	−27.0	−24.4	−16.9
Month 2	−38.4	−28.3	—	—	—	—	—	—	—
Month 3	—	—	—	−23.3	−24.3	—	—	—	—
Month 6	—	—	−17.6	−27.3	−26.4	—	—	—	—
Month 12	—	—	—	−29.2	−29.6	—	—	—	—

- Calculated based on data from Table 38 (*1), Table 40 (*2), and Table 43 (*3) in Review Report of Dayvigo Tablets.

vi) Intercurrent events

Treatment discontinuations, which could be considered intercurrent events potentially, affecting the interpretation or availability of endpoint measurements, did not occur in Studies SYK02 and S02. During the follow-up period after treatment completion in Study SYK02, treatment discontinuation occurred in 1 patient (1 of 87 patients; 1.1%). In addition, no use of prohibited concomitant drugs/therapies was reported in Studies SYK02 and S02. The above data indicate

that the effects of intercurrent events, potentially affecting the interpretation or availability of endpoint of measurements are minimal, and it is considered possible to perform the comparative evaluation.

vii) Number of participants/patients (sample size)

The sample size for Study S02 was predetermined and appropriately set to provide a basis (benchmark) for explaining the efficacy of the SUSMED App. In general, there is a risk of reduced statistical power associated with a small sample size, which may lead to a situation where the sample size is not large enough to detect a statistically significant difference. However, this does not necessarily affect the reliability of the obtained results. Although the setting of the α error (type I error)—the 5% probability that a significant difference between groups may be detected erroneously—remains unchanged, in this comparative evaluation the sample size may have been smaller than the sample size usually assumed to achieve a statistical power of 80% to 90%. As a result, there is a higher probability of a β error (type II error), which means that even if an effect exists, it may be difficult to demonstrate it (i.e., the risk of false negatives increases). This cannot be ruled out as a potential effect on reliability. On the other hand, in this comparative evaluation, the efficacy of the SUSMED App compared with zolpidem tartrate was successfully detected as statistically significant indicating that sample size did not have an impact on reliability.

Small sample sizes tend to increase variability in endpoints (e.g., mean change in AIS), raising the concern that in this comparative analysis, a statistically significant result was detected by chance. However, the statistical analysis methods account for this variability based on the assumptions underlying each test. In addition, as discussed in Sub-section "(b) Considerations for statistical analysis," the results of multiple statistical analysis methods together with each 95% confidence interval were presented from the standpoint of sensitivity analysis. The analysis results demonstrated robustness regardless of the statistical methods selected. Therefore, even considering the possibility that a statistically significant difference was detected by chance due to the small sample size, it is still considered possible to evaluate the comparative analysis. However, because all the analyses are based on the data of 19 patients from Study S02, the extent to which the randomness of data from these 19 patients can be explained is limited to what can be captured within 95% confidence intervals.

6.B.(1).2).(b) Considerations for statistical analysis

i) Pre-specification of the statistical analysis plan

The protocol of Study S02 was created on [redacted], 20[redacted] and fixed prior to the start of Study S02. Meanwhile, the protocol of the comparative analysis study for Studies SYK02 and S02, which was used for the present application, was created on [redacted], 20[redacted]. To avoid dependence

on a specific statistical analysis method, sensitivity analysis results were obtained by multiple analysis methods and presented with 95% confidence interval values. The robustness of the analysis results was demonstrated as follows:

- Table 26 shows the results obtained using different statistical methods with no covariate adjustment required. The conclusions remained consistent regardless of the statistical methods selected.
- The results were obtained by IPTW when covariate adjustment was required. The conclusions remained consistent.

Table 26. Sensitivity analysis results without adjustment with covariates (results obtained using different statistical methods)

						Change in AIS from baseline to Week 8 (end of treatment)			Change in AIS from baseline to Week 10 (2 weeks after treatment completion)			Change in AIS from Week 8 (end of treatment) to Week 10 (2 weeks after treatment completion)		
Test method	Summary	Normality	Homogeneity of variance	Type	Statistic calculated	Statistic	*P*-value	95% CI	Statistic	*P*-value	95% CI	Statistic	*P*-value	95% CI
Welch's t-test	A test for a difference in means (a parametric method that does not assume homogeneity of variance, but assumes normality)	Assumed	Not assumed	t-test (difference in means)	Difference in means	3.2	0.001	1.5 to 5.0	0.4	0.734	-1.9 to 2.6	-2.9	0.004	-4.7 to -1.0
Wilcoxon rank sum test (Mann-Whitney U-test)	A test for a difference in medians (a non-parametric method that does not assume normality but assumes homogeneity of variance)	Not assumed	Assumed	rank test	Difference in medians	3.5	0.001	1.0 to 6.0	0.5	0.615	-2.0 to 3.0	-2.5	0.000	-4.0 to 0.0
Yuen-Welch test	Welch's t-test is performed after trimming (excluding) N% at the lower tail and at the higher tail of the population * Trimming at the lower 10% and higher 10% was selected for the calculation presented	Assumed	Not assumed	t-test (difference in means)	Difference in trimmed means	3.1	0.002	1.2 to 4.9	0.5	0.550	-1.2 to 2.2	-1.8	0.007	-3.1 to -0.6
Bootstrap test	A Welch's t-test using the bootstrap method * The sample size for the bootstrap method was 100,000	Not assumed	Not assumed	t-test (difference in means)	Difference in means	3.3	0.001	1.5 to 5.1	0.4	0.741	-1.8 to 2.6	-2.9	0.018	-5.0 to -0.7
Brunner-Munzel test	A test for equality of the population distribution of 2 unpaired samples (a nonparametric method that does not assume normality or homogeneity of variance)	Not assumed	Not assumed	rank test	P (X < Y) + 0.5 × P (X = Y) * Probability of Y (control) being greater	0.3	0.000	0.2 to 0.4	0.5	0.606	0.3 to 0.6	0.7	0.001	0.6 to 0.9

ii) Statistical methods used in externally controlled trials

As discussed above, Studies SYK02 and S02 were conducted in study populations substantially identical to each other. The endpoints, observation period including the intervention period, concomitant drugs/therapies, etc. were also the same. In addition, possible confounding factors that may have affected the estimation of treatment effects were closely examined when the study plans were developed and implemented. Therefore, it was considered unnecessary to adjust for confounding factors in this evaluation, and unadjusted results are presented. In addition, there were differences between the studies, for instance, patients aged ≥65 years were not enrolled in Study S02; therefore, the results were adjusted by IPTW based on propensity score with age, sex, and baseline as covariates. The results demonstrated the robustness of the comparative analysis results.

iii) Addressing limitations of data and comparisons

In Study S02, there were no cases of "follow-up examinations not implemented or were performed outside the specified time window." Furthermore, Studies SYK02 and S02 established the same primary and secondary endpoints in their study protocols. For these reasons, there were no data required for analysis that were not collected; all data necessary for the analyses were collected. In Study SYK02, only 1 patient (1 of 87 patients, 1.1%) discontinued the study during the follow-up period after completion of treatment. It is not considered that this will affect the interpretation of the comparative analysis results.

PMDA's view:

The comparative analysis submitted by the applicant for the present application, is not a parallel-group study that directly compares the SUSMED App and zolpidem tartrate. Instead, it evaluates outcomes in the active group in Study SYK02 using the results from Study S02 as external control data.

When comparing the results of the comparative analysis conducted by the applicant with a hypothetical case in which a prospective, parallel-group study was conducted, the inclusion/exclusion criteria applied to the 2 groups are essentially identical, and Study S02 was conducted at the same study sites at which Study SYK02 was conducted. In addition, Study S02 was planned and started before the results of Study SYK02 became available, and therefore the results of S02 could not have been intentionally adjusted based on the results of Study SYK02. Based on these factors, while it is acknowledged that the applicant accounted for some biases that are generated when using external controls, the comparative analysis study has some inherent limitations:

- Study S02 was conducted by the developer of the SUSMED App with the intention of evaluating the device; therefore, the possibility that conscious/unconscious biases could arise cannot be ruled out.
- The protocol for re-analysis for the comparative analysis study was created after the results of the 2 studies used for the analyses became available. In addition, the endpoints the applicant claims show the superiority of the SUSMED App (e.g., change in AIS from Week 8 [end of treatment] to Week 10 [2 weeks after treatment completion], and the necessity of pharmacological treatment) differ from the primary endpoints of both studies. The possibility that these endpoints were selected post-hoc cannot be ruled out.
- In both studies, the sample size was not considered sufficient to test for key analysis items related to the efficacy and other aspects of the SUSMED App and zolpidem tartrate.
- In Study S02, administration of zolpidem tartrate was stopped at Week 8. However, according to the package insert of zolpidem tartrate, abrupt dose reduction or discontinuation after prolonged use may cause withdrawal symptoms and careful tapering is required when stopping treatment. In clinical practice, generally, medication is tapered by taking smaller doses, taking only when needed, and finally stopping completely. Therefore, it is likely that the results of Study S02 may not be generalizable to routine clinical practice or to the outcomes of pharmacotherapy approved in Japan.

Based on the above, it is difficult to draw conclusions regarding the superiority or inferiority of the SUSMED App compared with zolpidem tartrate based on the submitted data from the comparative analysis. However, because the findings of the comparative analysis can be regarded as information that helps to organize the characteristics of the SUSMED App and sleep medications, the efficacy of the SUSMED App will be discussed later in Section "6.B.(2) Efficacy of SUSMED App."

6.B.(2) Efficacy of SUSMED App

In Japan, in pharmacotherapy for insomnia, it is advised that doses should be tapered or interrupted as soon as remission is achieved. After pharmacotherapy is administered for a certain period of time, its effectiveness is assessed and, if necessary, the dose is reduced or the medication is interrupted. Conversely, if pharmacotherapy is discontinued before remission is reached, insomnia may recur or worsen, in which case, pharmacotherapy needs to be resumed.

Based on the above, PMDA considers it necessary to evaluate efficacy in 2 ways: effectiveness up to the first assessment after the initial prescription (hereinafter referred to as "Cycle 1 efficacy") and the overall effectiveness throughout the entire course of treatment from the initiation to the completion of treatment (hereinafter referred to as "long-term efficacy").

6.B.(2).1) Cycle 1 efficacy

In this comparative analysis study, the Cycle 1 efficacy of zolpidem tartrate was compared with that of the SUSMED App. The applicant's explanation about the efficacy of the product:

It cannot be concluded that statistical equivalence and non-inferiority were demonstrated based on the data for change in AIS from baseline to Week 10 (2 weeks after treatment completion) (Table 10), change in AIS item-by-item (Table 13), proportion of patients with an AIS <6 points (Table 16), change from baseline in sleep onset latency, sleep efficiency, and the number of nocturnal awakenings (sleep logs/actigraph data) (Table 20 and Table 21). During the treatment period, the improvement in insomnia symptoms was statistically significant in the zolpidem tartrate group compared with the App group from baseline to Week 8 (end of treatment) (Table 12). However, the results from baseline to Week 10 (2 weeks after treatment completion) do not show a statistically significant difference for any of the endpoints including change in AIS (Table 13). In addition, improvements in some items[viii] tended to be greater in the App group, while improvements in other items[ix] tended to be greater in the zolpidem tartrate group. Overall, the degrees of improvement were comparable between the groups.

Furthermore, from Week 8 (end of treatment) to Week 10 (2 weeks after treatment completion), the AIS score change (Table 11) and the AIS item-by-item changes—except for "awakening earlier than desired and unable to fall back to sleep" and "sleepiness during the day" (Table 14)—showed significantly greater improvement in the App group than in the zolpidem tartrate group. The proportion of patients with an AIS of <6 points (Table 17) increased from 37.9% to 48.8% in the App group while the proportion decreased from 73.7% to 57.9% in the zolpidem tartrate group. Change in CGI-I, a physician assessment at Week 8 (end of treatment), improved statistically significantly in the zolpidem tartrate group compared with the App group (Table 18). Conversely, the proportion of patients for whom medication was deemed necessary as assessed by the physician at Week 10 (2 weeks after treatment completion) improved statistically significantly in the App group compared with the zolpidem tartrate group (Table 19).

Furthermore, in clinical practice, prolonged therapeutic effects and remission after completion of treatment are not confirmed solely by assessing changes observed at specific post-treatment timepoints. Instead, whether the patient needs to be re-treated or not (recovery) is

viii Change in AIS (sleep induction, overall quality of sleep, sleepiness during the day), sleep onset latency (sleep logs/actigraph data), sleep efficiency (sleep logs/actigraph data)

ix Change in AIS (total, awakenings during the night, awakening earlier than desired and unable to fall back to sleep, sense of well-being during the day, physical and mental functioning capacity during the day), proportion of patients with AIS <6 points, the number of nocturnal awakenings (sleep logs/actigraph data)

comprehensively evaluated by considering the change in insomnia symptoms and results after treatment. Therefore, the efficacy of the SUSMED App should also be evaluated as described above. Based on the results of the comparative analysis, if patients have achieved recovery through a course of treatment using the SUSMED App, or even if only remission is achieved, such outcomes are clinically meaningful if sustained for a long period of time. It has been suggested that longer duration of pharmacotherapy leads to an increase in adverse reactions such as rebound insomnia, withdrawal symptoms, and resistance, which makes it difficult for patients to recover from insomnia. Therefore, if the patient recovers from insomnia after completion of a course of treatment using the SUSMED App in the initial treatment cycle, the patient may choose pharmacotherapy and take sleep medication for the first time in Cycle 2 or subsequent cycles. This reduces the risks associated with prolonged pharmacotherapy.

Based on the above, it is considered that the SUSMED App has demonstrated clinically meaningful efficacy in Cycle 1.

6.B.(2).2) Long-term efficacy

To compare the therapeutic effect of the SUSMED App with that of zolpidem tartrate, PMDA asked the applicant to explain why improved symptom lasted even after completion of treatment with the product.

The applicant's explanation:

The SUSMED App is designed based on the concept of CBT-I. Because of the therapeutic mechanisms of CBT-I, its effects are known to persist after completing treatment, leading to improved remission rates. The treatment guidelines established in the US and Europe clearly state that the treatment effects of CBT-I persist for a prolonged period after treatment ends, a view which has gained an international consensus[8] (Table 27). In meta-analyses and other studies, software as a medical device for insomnia available in the overseas market, such as Somnio[9, 10] and Somryst,[11] which have design concepts similar to that of the SUSMED App, showed sustained long-term effects at 3 months, 6 months, and 1 year after the completion of treatment as well as improvement in remission rates.

Table 27. Long-term effects of CBT

Guidelines/studies	Description
US guidelines	Treatment effects persist over the long term after completing treatment without the need for additional interventions
European guidelines	A major advantage of CBT-I is its long-lasting effects. This is in contrast to pharmacotherapy in which symptoms frequently recur or even rebound after treatment discontinuation. Such effects have not been reported for CBT-I. As suggested by the evidence from multiple studies and publications, the effects of CBT-I (Tables 6 to 8 in the guidelines) stabilizes over time (follow-up studies of up to 10 years have been published).
Study cited in the European guideline	Based on a 6-week self-guided CBT-I program, the therapeutic effects in the guided group were compared with those in the unguided group. Therapeutic effects lasted for a prolonged period after the completion of treatment. • Evaluation timepoints: immediately after completion of treatment, 1 year, and 10 years after completion of treatment • Endpoints: ISI, use of sleep medications, number of patients diagnosed as having insomnia
Study cited in the European guideline	Systematic review, meta-analysis The effects of digital CBT-I were compared with the waitlist group at Week 5 (2 studies), Week 6 (8 studies), and Week 9 (2 studies). Insomnia was improved significantly in the digital CBT-I group, with the therapeutic effects lasted for a prolonged period after completion of treatment. • Evaluation timepoints: immediately after completion of treatment, 4 weeks to 1 year after completion of treatment • Endpoints: ISI, sleep efficiency, severity of depression
Study (1)[12]	Meta-analysis The medium-term therapeutic effects (4 to 8 weeks) of CBT for insomnia was significantly high compared with control. The long-term therapeutic effects (3- to 12-month follow-up study) were markedly evident. In the CBT for insomnia group, clinical benefits were well maintained over a prolonged period, whereas the effects in the control group returned to baseline after completion of treatment.
Study (2)[13]	Meta-analysis Digital CBT-I improved insomnia significantly compared with control and these improvements lasted for 1 year, showing long-term efficacy comparable to that of face-to-face CBT-I.

Figure 4 shows the time course of changes in AIS in the App group and the sham app group in Study SYK02. During the intervention period, from baseline to Week 8 (end of treatment), improvement was greater in the App group than in the sham app group. The improvement was sustained between Week 8 (end of treatment) and Week 10 (2 weeks after treatment completion). This time course of changes in AIS was similar to the results (time course change in insomnia severity index [ISI][x], Figure 5) for a similar product, Somnio, available in the overseas market. Both the SUSMED App and Somnio are software as a medical device based on the concept of CBT-I, and have a similar mechanism of treatment. This suggests that the effectiveness of the SUSMED App observed at Week 10 (2 weeks after treatment completion) will persist as long as

x The AIS consists of 8 items with scores ranging from 0 to 24 (each AIS item 0-3). The ISI is a scale measuring a total of 7 items ranging from 0 to 28 (each item 0-4). A strong positive correlation has been suggested between the AIS and ISI.

that of Somnio or longer. Therefore, based on the results of Study SYK02, it is considered that the SUSMED App has long-term efficacy.

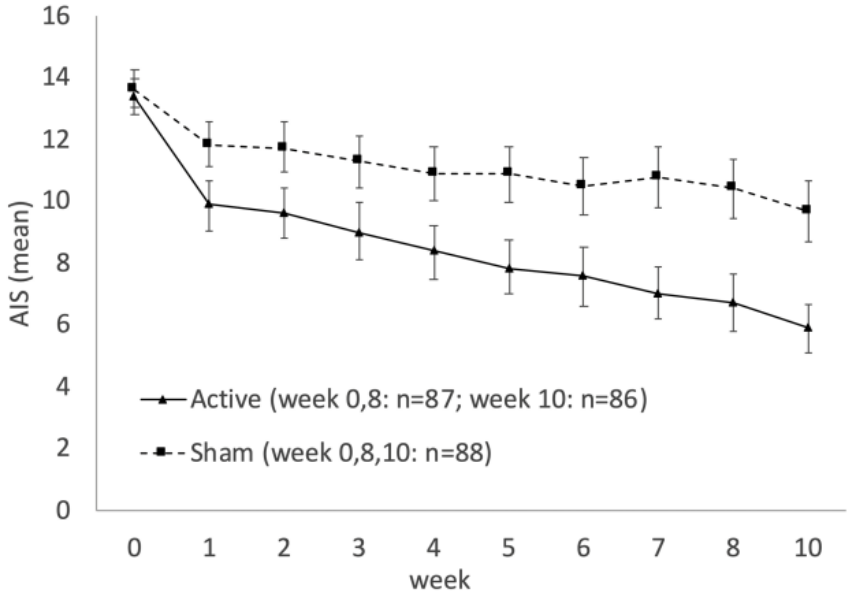

Figure 4. Time course of changes in AIS in the App (active) group (Study SYK02)

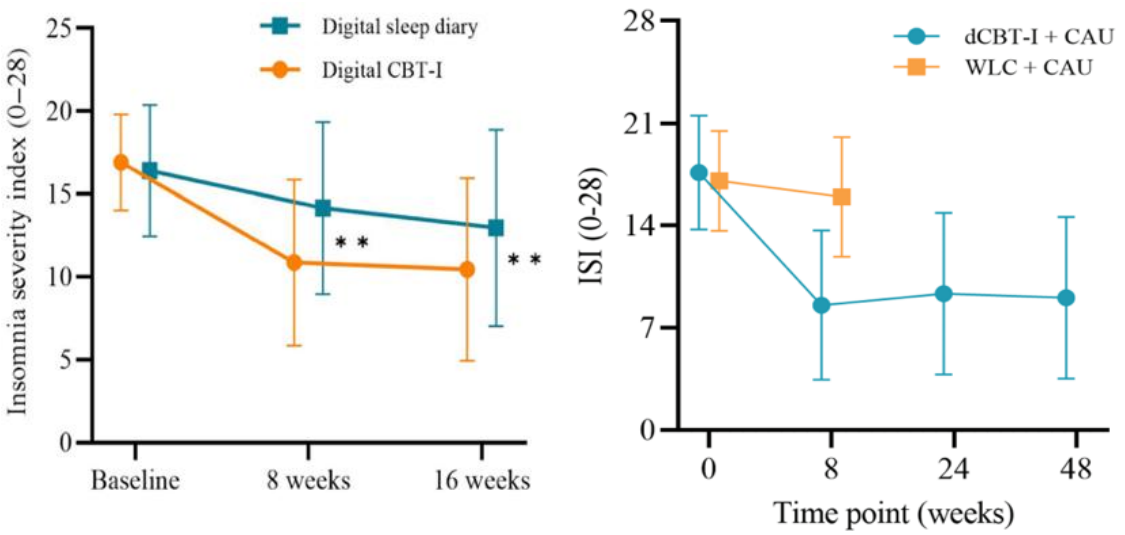

Figure 5. Time course of changes in ISI for Somnio

Digital sleep diary: group that used digital sleep diary
Digital CBT-I: group that used Somnio
dCBT-I + CAU: Somnio + care-as-usual
WLC[xi]+ CAU: waitlist control + care-as-usual

PMDA asked the applicant to explain the appropriateness of selecting zolpidem tartrate as the

[xi] A waitlist control (WLC) group is a group of participants who are on a waiting list and do not immediately receive intervention in a clinical study, etc. The participants are to receive the same intervention later. A WLC group is established to reduce dropouts for ethical reasons and to allow comparison of intervention effects.

control to evaluate the clinical utility of the SUSMED App.

The applicant's explanation was as follows.

1) Prescription status

The prescription trends in sleep medications for insomnia in clinical practice in Japan have been analyzed based on the receipt data, health examination data, and the ledgers of insured persons (and their family members) under the Health Insurance Association. Among medications prescribed in 2019, the most recent data in the report, the most frequently prescribed class of drugs are Z-drugs (a collective term for zolpidem tartrate, zopiclone tablets, and eszopiclone tablets), which accounted for 40.2%, followed by benzodiazepines at 32.1%. In the report, the total of benzodiazepine receptor agonists accounted for 72.3%.[14]

2) Efficacy

While zolpidem tartrate is a benzodiazepine receptor agonist, other sleep medications include melatonin receptor agonists. In the Investigative Research on Receipt Analysis Contributing to Policy Making III released in October 2017, melatonin receptor agonists are classified as medications with a highly favorable safety profile but with lower efficacy. Orexin receptor antagonists are medications shown to be effective in treating nocturnal awakening and early morning awakening. In addition, according to systematic reviews (network meta-analysis), zolpidem tartrate has a greater acute effect (effectiveness after 4 weeks of treatment) compared with the melatonin receptor agonists Rozerem Tablets (ramelteon) and Melatobel Tablets (melatonin), as well as orexin receptor antagonists such as Dayvigo Tablets (lemborexant), Quviviq Tablets (daridorexant hydrochloride), which are.[15] Each sleep medication profile has its own distinct characteristics, and in clinical practice, medications are selected based on these characteristics.

Regardless of differences in the mechanism of action, a common feature of all sleep medications is that their treatment effects are exerted only during the time these medications are being taken. In the Review Report of Quviviq Tablets, an orexin receptor antagonist launched in December 2024, the primary endpoint to evaluate efficacy in insomnia—the change in subjective sleep onset latency from baseline to Week 4—was −5.9 (placebo), −13.0 (Quviviq 25 mg), and −16.5 (Quviviq 50 mg). At Week 5 (1 week after treatment completion), the changes from baseline were −8.1 (Quviviq 25 mg) and −6.3 (Quviviq 50 mg). In other words, the improvement in insomnia immediately after administration of Quviviq Tablets (Week 4) was roughly halved just 1 week after treatment ended. This indicates that, based on the therapeutic mechanism, it is considered difficult to achieve sustained effects or improved remission rates after the completion of treatment.

Sustained effects and improvement in remission rates after the completion of treatment were demonstrated in the App group compared with the zolpidem tartrate group in the comparative analysis. It is considered that, because of the therapeutic mechanism, these effects and improvements in remission rates will also be demonstrated not only compared with benzodiazepine receptor agonists including zolpidem tartrate but also sleep medications in general, such as melatonin receptor agonists and orexin receptor antagonists.

3) Safety

Table 28 summarizes the differences in safety between the SUSMED App and sleep medications (Rozerem Tablets, Dayvigo Tablets, and Quviviq Tablets).

In Study SYK02, no adverse reactions or malfunctions were reported with the SUSMED App. Since the initial approval of the device, no safety concerns have been identified that would pose any particular issues.

Meanwhile, for Rozerem Tablets, a melatonin receptor agonist, the package insert lists contraindications and adverse reactions such as somnolence and sleepiness.[16] Therefore, careful consideration is required regarding t safety issues and patient populations when using the drug.

Similarly, for Dayvigo Tablets, an orexin receptor antagonist, the package inserts lists contraindications and adverse reactions such as somnolence, headache, and dizziness.[17] In addition, in a global phase III clinical study (Study 303), the incidence of adverse reactions was 28.2% (249 of 884 patients). For Quviviq Tablets (daridorexant hydrochloride), another orexin receptor antagonist, the package insert lists contraindications and adverse reactions such as somnolence and dizziness.[18] In addition, in a Japanese phase III clinical study, the incidence of adverse reactions was 7.4% at 25 mg and 11.1% at 50 mg.

Therefore, it is considered that the results of the safety evaluation of the SUSMED App, which are based on a comparison with zolpidem tartrate, will not change markedly even if compared with other pharmacotherapies for insomnia used in clinical practice.

Table 28. Differences between SUSMED App and sleep medications in terms of safety

		SUSMED App	Melatonin receptor agonist	Orexin receptor antagonists	
			Rozerem Tablets	Dayvigo Tablets	Quviviq Tablets
WARNINGS		• Precautions: the product should be used in an appropriate manner in compliance with the proper-use guidelines developed by the relevant academic societies	—	—	—
Contraindications		—	• Patients with a history of hypersensitivity to any ingredients of the product • Patients with severe hepatic impairment • Patients receiving fluvoxamine maleate	• Patients with a history of hypersensitivity to any ingredients of the product • Patients with severe hepatic impairment	• Patients with a history of hypersensitivity to any ingredients of the product • Patients with severe hepatic impairment (Child Pugh C) • Patients receiving any of the following: itraconazole, clarithromycin, voriconazole, posaconazole, ritonavir-containing regimen, cobicistat-containing regimen, ceritinib, and ensitrelvir fumarate
Adverse reactions	Incidence	0%	(Unknown)	Global phase III study: 28.2%	Japanese phase III study • 7.4% (25 mg) • 11.1% (50 mg)
Adverse reactions	Event	—	e.g., somnolence, sleepiness, headache	e.g., somnolence, headache, malaise, sleep paralysis, dizziness	e.g., somnolence, dizziness, pyrexia

Based on points 1), 2), and 3) above, it is considered appropriate to conduct a comparative study by setting zolpidem tartrate as the standard of care in order to compare the SUSMED App with sleep medications, which present challenges in the treatment of insomnia.

The SUSMED App is medical application software for the treatment of insomnia. The product is aimed to enable medical institutions and physicians treating insomnia, regardless of their departments or specialty, etc., to provide non-pharmacological intervention without causing further staff shortages, an ongoing challenge in clinical settings in Japan. Study SYK02 was conducted at [redacted] specialized [redacted] and [redacted] other non-specialized facilities. As shown in Table 29, no trends for varying change in AIS, the primary endpoint, were observed among the facilities. Study SYK02 revealed neither adverse events for which a causal relationship to the SUSMED App could not be ruled out nor malfunctions. Thus, the efficacy and

safety of the SUSMED App were demonstrated regardless of the departments or specialty, etc. of treating physicians, as intended in the product development.

Table 29. Change in AIS by study site in Study SYK02

Analysis population: mITT population
Imputation method: none

			Baseline	Week 8	Change from baseline				
Category	Group	N	Mean	Mean	Mean	Min	Median	Max	SD
[redacted]									

PMDA's view:

As discussed earlier in Section "6.B.(1) Comparative study submitted," in Study S02, administration of zolpidem tartrate was stopped at Week 8. Generally in clinical practice, medication is tapered off toward treatment completion after occasional as-needed doses. Therefore, the results of Study S02 may not fully reflect pharmacotherapy in clinical practice. Medications for insomnia used in clinical practice other than zolpidem tartrate include those that are less likely to cause rebound insomnia (e.g., melatonin receptor agonists and orexin receptor antagonists). Nevertheless, as explained by the applicant, the results of Study S02 do not differ significantly from clinical data on other sleep medications, and it is possible to examine the

efficacy- and safety-related characteristics of the SUSMED App and sleep medications including zolpidem tartrate based on the results from Studies SYK02 and S02.

The stimulus control therapy and sleep restriction therapy with the SUSMED App allow patients to systematically manage their behavior around sleep and sleep onset to a certain extent based on their own condition recorded in the sleep diary, etc. Therefore, it is considered possible to examine information on face-to-face CBT-I and similar overseas products as well.

Given the time course of changes in AIS in the App group (Figure 5) observed in Study SYK02 and the fact that the SUSMED App was developed based on the CBT-I concept for the SUSMED App, it can be expected that the SUSMED App will improve insomnia symptoms in a sustained way by correcting lifestyle and sleeping habits rather than by having an immediate effect; i.e., it may take longer for the effects to manifest. Although improvement in the change in AIS is more significant in the zolpidem tartrate group than in the App group at Week 8 (end of treatment), the difference between groups became smaller at Week 10 (2 weeks after treatment completion). In addition, 26.3% of patients in the zolpidem tartrate group were assessed as still requiring pharmacotherapy at Week 10 (2 weeks after treatment completion) while in the App group, pharmacotherapy was required in only 7.0% of patients (Table 19), suggesting that the SUSMED App tended to maintain its effectiveness for a longer period. The comparative analysis results and their interpretation as described above are broadly consistent with the findings for face-to-face CBT-I, supporting the view that the SUSMED App alone can also be expected to have long-term efficacy.

Based on the above, the SUSMED App has shown a certain level of efficacy by itself for the treatment of insomnia in patients who do not require immediate improvement.

6.B.(3) Clinical positioning

The applicant's explanation about proper choice between the SUSMED App or pharmacotherapy in view of the clinical positioning of the SUSMED App:

Table 30 summarizes the characteristics of the SUSMED App and pharmacotherapy. Treatment guidelines for insomnia in other countries define non-pharmacologic interventions, i.e., radical treatment, as first-line treatment, and pharmacotherapy, a symptomatic treatment, as second-line treatment. The SUSMED App is a programmed medical device providing non-pharmacologic therapy for insomnia based on CBT-I, a radical treatment. Several studies have shown the therapeutic effects of the SUSMED App lasting even after treatment completion as compared to pharmacotherapy, contributing to improved remission rates. The effects are expected to last for

up to 6 months or 1 year, and therefore, the product can be regarded as a treatment option for insomnia. In eligible patients, the use of the SUSMED App prior to or in combination with pharmacotherapy will help realize the proper use of pharmacotherapy for insomnia.

Table 30. Characteristics of SUSMED App and pharmacotherapy

	SUSMED App	Pharmacotherapy
Efficacy	Treatment approach that potentially addresses the root causes of insomnia with sustained treatment effect • The long-term effects of CBT, the concept underlying the SUSMED App, are recognized as the international standard • Factors contributing to the long-term effects of CBT, commonly cited in the European/US guidelines (core CBT techniques) are sleep restriction therapy and stimulus control therapy • Sleep restriction therapy and stimulus control therapy are reproduced in the intervention with SUSMED App • The comparative analysis revealed that maintenance of treatment effect and increase in remission rates in the App group were more significant compared with pharmacotherapy in the 2 weeks following the completion of treatment (significant improvement in the change in AIS; time course change in AIS tended to be maintained or improved; proportion of patients with AIS <6 points was maintained/improved; proportion of patients for whom medication was deemed unnecessary as assessed by physician at 2 weeks after treatment completion was higher) • The functions of the SUSMED App (including the core CBT techniques) were almost the same as those for Somnio, which is covered under medical reimbursement in Germany as digital CBT for insomnia, and long-term efficacy for approximately 1 year after the completion of treatment has been demonstrated (only the progressive muscle relaxation method has not been implemented in the SUSMED App) • The progressive muscle relaxation (relaxation) method is described as ineffective in the European/US guidelines. It is not considered a function that contributed to the recognition of CBT's long-term effects as the global standard.	Symptomatic therapy with short-term effects (no long-term effects) • No long-term effects according to the Japanese and European guidelines. • In the European/US guidelines, pharmacotherapy is defined as second-line treatment, and short-term use (1-3 months) is recommended. • Because the duration of the effects of a drug depends on the drug's half-life, the therapeutic effect dissipates after dosing is interrupted in accordance with the half-life. • Sleep medications have half-lives ranging between 1 and 85 hours. They have a quick onset of action and a short duration.
Safety	Exceptionally high safety profile. No adverse reactions were reported in Study SYK02.	For each drug, multiple contraindications are established; drug dependence, withdrawal symptoms, etc. are reported as "clinically significant adverse reactions" for some drugs; many cases of adverse reactions have been reported.

Pharmacotherapy is a symptomatic treatment with risks of adverse reactions such as rebound insomnia and withdrawal symptoms. However, because of its immediate effect, pharmacotherapy can treat patients with high medical urgency or severe illnesses, or for those inadequately responding to the SUSMED App intervention, based on the benefit-risk balance.

Taken together, it is considered appropriate to use the SUSMED App prior to or in combination with pharmacotherapy for patients with mild to moderate insomnia taking no or 1 sleep medication who do not have psychiatric disorders, according to the proper use guidelines. Despite its immediate effect, pharmacotherapy involves safety risks and, therefore, should be used for patients with high medical urgency or severe insomnia (taking ≥2 types of sleep disorder medications; having psychiatric disorders) or those inadequately responding to the SUSMED App intervention.

PMDA's view:
The applicant explains that it is appropriate to use the SUSMED App prior to or in combination with pharmacotherapy for eligible population. The known causes of sleep difficulty include difficulty maintaining sleep because of attenuated function of neural mechanisms (sleep center) to induce sleep, causing shallow unstable sleep; difficulty falling asleep due to delayed circadian rhythm that delays sleep hours; early-morning awakening due to delayed circadian rhythm that advances sleep phase; sleep onset insomnia due to hyperarousal mechanism (arousal center) that keeps the person wide awake. For patients with these symptoms, pharmacologic approaches are more effective to modulate sleep. As described earlier in Section "6.B.(2) Efficacy of SUSMED App," the time to onset, level, and duration of the effect of the SUSMED App are suggested to differ from those of zolpidem tartrate that has immediate effects. In Study SYK02, no adverse reactions or malfunctions were reported. The submitted clinical study data indicated no clear risks for patients eligible for the SUSMED App.

Based on the above, the SUSMED App can be regarded as a new option of non-pharmacological treatment for patients with eligibility for Study SYK02, namely, those with insomnia poorly managed through sleep hygiene education alone. Although no data showing the efficacy and safety of the SUSMED App used with pharmacotherapy have been submitted, the Japanese Clinical Guidelines assume the use of the SUSMED App in combination with pharmacotherapy, standing on the CBT-I-based design concept of the product. Because of no clear risk identified in Study SYK02 for patients who used the SUSMED App, it is not necessary to restrict the combination use of the SUSMED App with pharmacotherapy. Despite its CBT-I-based design with some CBT-I functions, the SUSMED App provides only standardized content as compared

to face-to-face CBT-I. Therefore, the product should not be regarded as equal to face-to-face CBT-I. Taking into account the discussions at the Expert Discussion, the SUSMED App will be regarded as a new treatment option for patients with insomnia poorly managed by sleep hygiene education alone, as for those receiving pharmacotherapy. The following modified intended use or indication are deemed appropriate.

Intended use

To support insomnia treatment

Among patients with secondary insomnia, there are patients who are not eligible for treatment with the SUSMED App due to the influence of the underlying disease. Therefore, the SUSMED App should be used only by physicians who have gained an understanding of characteristics of CBT-I, have sufficient knowledge on the limitations of the SUSMED App, and are able to accurately assess the patient's condition. In particular, due to unknown efficacy or safety of the SUSMED App against chronic insomnia comorbid with psychiatric disease, this patient population should be excluded from the indication for the SUSMED App. Eligibility for the treatment with the SUSMED App must be carefully determined individually by referring to the proper use guidelines (Table 31). Accordingly, PMDA has concluded that partial change approval should be granted with the approval conditions as per the initial approval.

Approval conditions

The applicant is required to ensure that the product is used only by physicians with adequate knowledge of insomnia, based on a thorough understanding of CBT-I and the product characteristics. To this end, necessary measures, including dissemination of the proper-use guidelines jointly developed with the relevant academic societies and provision of training programs, should be taken.

While the SUSMED App was designed based on the concept of CBT-I, the product does not contain the same content as face-to-face CBT-I as mentioned above, and physicians and users should be clearly aware of this. At the time of the initial approval, the product's brand name was "SUSMED Med CBT-i App for Insomnia." PMDA asked the applicant to reconsider the brand name, out of concern for a possible misperception that the product would provide intervention equivalent of face-to-face CBT-I.

In response, the applicant changed the brand name to "SUSMED App for Insomnia Medcle." PMDA accepted the brand name.

Table 31. Outline of proper use guidelines

	Outline
Intended patients	Patients must meet all the following requirements: 1) Diagnosed as having insomnia disorder (insomnia) 2) Experiencing mild to moderate insomnia symptoms 3) Not meeting any of the exclusion criteria
Ineligible patients	In principle, patients who meet any of the following requirements are ineligible. If patients are found to violate any of the criteria during use, the use of the app should be terminated. 1) Having severe insomnia 2) Taking ≥2 types of sleep disorder medicines 3) Having a psychiatric disorder 4) Having a moderate or more severe physical disorder 5) Having a sleep-wake disorder other than insomnia 6) Engaged in shift or night work 7) Any other condition deemed inappropriate by the physician providing treatment with the SUSMED App
Requirements for physicians who provide treatment with the SUSMED App	The physician must meet at least one of the following requirements: 1) Completed a cognitive behavioral therapy for insomnia (CBT-I) program offered by any of the following organizations: Japanese Society of Sleep Research, Japanese Association for Cognitive Therapy, Japanese Association of Behavioral and Cognitive Therapies, and National Center of Neurology and Psychiatry 2) Completed the training program on the proper use of the SUSMED App

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

In the Review Report of the SUSMED App at the initial approval, the applicant was required to conduct post-marketing surveillance for the following reasons:

> In the pivotal clinical study and exploratory study, there were no adverse events for which a causal relationship to SUSMED App could not be ruled out and no malfunctions leading to serious adverse events. Meanwhile, the cognitive therapy incorporated in SUSMED App only visualizes worries and thoughts, without providing cognitive intervention to correct insomnia-associated thinking. Therefore, this lack of appropriate action to address the worries or thought patterns may worsen insomnia symptoms. (excerpted from Review Report for initial approval)

Based on the above, the safety of the SUSMED App in clinical use should be further assessed through a use-results survey as practiced after the initial approval, and proper product use should be ensured by necessary measures taken. Accordingly, the applicant submitted the use-results survey plan that took over the one at the time of the initial approval (Table 32).

Table 32. Outline of use-results survey (draft) formulated at the time of initial approval

Objective	To confirm the safety and efficacy of SUSMED App in clinical practice
Population	Patients with insomnia
Planned sample size	300 patients
Number of sites	20
Survey period	Three years and 11 months from the date of marketing approval (preparation period, 1 year;

	enrollment period, 2 years; follow-up period, 8 months at the maximum; analysis period, 3 months)
Survey items	Safety such as adverse events, malfunctions of SUSMED App, long term safety and efficacy (key survey items: safety in patients excluded from the clinical studies [e.g., patients with secondary insomnia])

7.B Outline of the review conducted by PMDA

Unlike sleep medications, the SUSMED App takes longer to show its effects, and therefore the product needs to be used constantly during the intervention period. Although acute adverse reactions such as those with sleep medications are unlikely to occur, it is not easy to correct cognitive distortions associated with the SUSMED App intervention once established, as mentioned in the Review Report of the SUSMED App at the initial approval.

As mentioned in the Review Report of the SUSMED App for initial approval, the intended patients are those who are eligible for face-to-face CBT-I as specified in the manual of cognitive behavioral therapy for insomnia prepared by the Japanese Society of Sleep Research. For the present application, eligible patients for the SUSMED App are those with insomnia poorly managed through sleep hygiene education alone. The SUSMED App can be regarded as a new non-pharmacologic treatment option for these patients, and the product is assumed to be prescribed by physicians from diverse fields for various patients compared to the time of initial approval. Given this situation, it is increasingly important for physicians to prescribe the SUSMED App with a good understanding of the product and the characteristics of CBT-I, the product concept.

The proper use guidelines developed at the time of the initial approval for the SUSMED App present the following 2 requirements to qualify physicians who provide treatment with the product:

- Physicians who completed a CBT-I training program organized by the relevant academic societies (hereinafter referred to as “academic society training”)
- Physicians who completed the training program on proper use of the SUSMED App (hereinafter referred to as “App training”)

It is highly likely that physicians who completed the academic society training are competent in using the SUSMED App properly, in view of the characteristics of CBT-I and differences between the SUSMED App and face-to-face CBT-I, etc. Conversely, it is assumed that physicians who were previously not particularly well-versed in face-to-face CBT-I but wish to use the SUSMED App are more likely to attend the App training program. The program provides CBT-I content, but content sufficiency is subject to further assessment after the product launch for ensuring

proper product use by physicians of this category.

Based on the above, assessment should be continued via the use-results survey to confirm that physicians who have attended the App training program are as competent in dealing with the product (Phase 1) as those who completed the academic society training. Based on the Phase 1 results, the App training program should be modified, or necessary measures should be taken to ensure thorough adherence to proper product use. The subsequent use-results survey (Phase 2) should continuously assess sufficiency of the measures taken for the App training program.

PMDA asked the applicant to reconsider the use-results survey plan taking into account the above-mentioned ideas.

The applicant agreed with the instruction and submitted the use-results survey plan (Table 33). PMDA accepted the plan.

Table 33. Outline of use-results survey (draft)

Type	Use-results survey
Objective	To confirm the safety and efficacy of SUSMED App in clinical practice
Population	Patients with insomnia
Survey period	Four years and 6 months from the date of partial change approval ■ Preparation period: 12 months ■ Phase 1 (data accumulation: case registration, follow-up period): 18 months ■ Phase 1 (interim analysis: 150 patients): 3 months ■ Phase 2 (data accumulation: case registration, follow-up period): 18 months ■ Phases 1 and 2 (final analysis: 300 patients): 3 months
Planned sample size	Total of 300 patients ■ Phase 1 (data accumulation: case registration, follow-up period): 150 patients Collecting data and information after entering into a contract with the medical institutions to which physicians who have completed the CBT-I training offered by the relevant academic societies belong (N = 75); collecting data and information after entering into a contract with the medical institutions to which physicians who have completed the training program on proper use of the SUSMED App belong (N = 75) ■ Phase 2 (data accumulation: case registration, follow-up period): 150 patients Collecting data and information after entering into a contract with the medical institutions to which physicians who have completed the training program on proper use of the SUSMED App belong (N = 150)
Number of sites	20
Key survey items	■ Safety such as adverse events when the SUSMED App is used ■ Safety and other aspects of patients who were ineligible to be included in the clinical study (e.g., patients with secondary insomnia) ■ Long-term efficacy

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

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

The medical device application data (Attached documents, *He*-1, 01_[*He* 1] Comparative re-

analysis study report_v1.0, and 05_[*He* 1] Comparative re-analysis study protocol_v1.1) were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

The SUSMED App is a software program for patients with insomnia poorly managed through sleep hygiene education alone, as for those receiving pharmacotherapy. This review primarily focuses on (1) efficacy and (2) clinical positioning of the SUSMED App. Taking into account the comments from the Expert Discussion, PMDA has reached the following conclusions.

(1) Efficacy of SUSMED App

The constraints in the evaluation design hinder the discussion about superiority or inferiority in the efficacy and safety of the SUSMED App against insomnia medications based on the submitted comparative analysis data. Yet, the characterization of the SUSMED App and insomnia medications such as zolpidem tartrate is considered possible.

Sleep medications have immediate effects but can cause adverse events at a certain rate. Once interrupted, their therapeutic effects diminish immediately. In contrast, the SUSMED App needs longer to exert its effect, but the product did not cause adverse events observed with sleep medications, while suggesting a sustained effect lasting even after the completion of intervention. The results are considered attributable to its CBT-I-based design that helps adjust patient's mindsets and behavioral patterns. Also, the SUSMED App has characteristics consistent with those reported from face-to-face CBT-I, indicating the product's certain long term efficacy that lasts even after the completion of intervention.

Based on the above, the SUSMED App has a certain level of efficacy by itself in the treatment of insomnia when it does not require immediate improvement as expected in sleep medications.

(2) Clinical positioning

As noted above, with the expected long-term efficacy and no safety concerns that could pose immediate problems, it is possible to regard the SUSMED App as a new treatment option for patients with insomnia poorly managed through sleep hygiene education alone, as for those receiving pharmacotherapy. However, the proper use guidelines should be continuously adhered to, and the appropriateness of the App training program should be assessed through the post-

marketing surveillance. In addition, the number of physicians competent in handling the product should be increased in stages.

As a result of its review, PMDA has concluded that the SUSMED App may be approved for the intended use shown below with the following approval conditions.

Intended Use
To support insomnia treatment

Approval Conditions
The applicant is required to ensure that the product is used only by physicians with adequate knowledge of insomnia, based on a thorough understanding of CBT-I and the product characteristics. To this end, necessary measures, including dissemination of the proper-use guidelines jointly developed with the relevant academic societies and provision of training programs, should be taken.

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 and the survey period should be 4 years and 6 months.

PMDA has concluded that the application should be deliberated at the Subcommittee on Software as a Medical Device.

References

1 MHLW Research Group and Japanese Society of Sleep Research Working Group “Clinical Practice Guidelines for Proper Use and Discontinuing Sleep Medications.”

2 Dieter Riemann, Colin A. Espie, Ellemarije Altena, Erna Sif Arnardottir, Chiara Baglioni, Claudio L. A. Bassetti, Celyne Bastien, Natalija Berzina, Bjørn Bjorvatn, Dimitris Dikeos, Leja Dolenc Groselj, Pierre A. Geoffroy, Elisabeth Hertenstein, Brigitte Holzinger, Heli Järnefelt, Susanna Jernelöv, Samson Khachatryan, Lukas Krone, Jaap Lancee, Damien Leger, Adrian Lupusor, Daniel Ruivo Marques, Christoph Nissen, Laura Palagini, Tiina Paunio, Lampros Perogamvros, Dirk Pevernagie, Manuel Schabus, Eus Van Someren, Johan Verbraecken, Tamar Shochat, Andras Szentkiralyi, Jason G. Ellis, Michaela Gjerstad, Diego Garcia-Borreguero, Marta Gonçalves, Kerstin Hoedlmoser, Tuuliki Hion, Markus Jansson-Fröjmark, Karolina Janku, Annemieke van Straten, Kai Spiegelhalder. The European Insomnia Guideline: An update on the diagnosis and treatment of insomnia 2023. J Sleep Res. 2023;32:e14035.

3 International Narcotics Control Board. Report of International Narcotics Control Board for 2010.

4 Kazuo Mishima, Masahiro Takeshima, Minori Enomoto. FY2020 Health and Labour Sciences Research Grants (Policy Research Project for Persons with Physical Disabilities) “Study report contributing the practice of exit strategy of psychiatric pharmacotherapy—appropriate continuation/dose reduction/discontinuation of psychotropic drugs” [in Japanese].

5 Central Social Insurance Medical Council General Meeting (579th). Chuikyo So-1-2: Health Technology Assessment (draft) [in Japanese]. https://www.mhlw.go.jp/content/12404000/001209379.pdf (accessed on July 1, 2025)

6 Kousei Miwa, Yoshinori Nishino, Mina Kikuchi, Takako Masue, Yoji Moriyama, Takashi Deguchi. Efficacy of combination therapy with tamsulosin and zolpidem on nocturia in patients with benign prostatic hyperplasia. Central European Journal of Urology 2011/64/4

7 Review Report of Dayvigo Tablets, November 2019

8 Jack D. Edinger, J. Todd Arnedt, Suzanne M. Bertisch, Colleen E. Carney, John J. Harrington, Kenneth L. Lichstein, Michael J. Sateia, Wendy M. Troxel, Eric S. Zhou, Uzma Kazmi, Jonathan L. Heald, Jennifer L. Martin, Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. Journal of Clinical Sleep Medicine, Vol. 17, No. 2

9 Jennifer Schuffelen, Leonie F. Maurer, Noah Lorenz, Alexander Rötger, Reinhard Pietrowsky and Annika Gieselmann. The clinical effects of digital cognitive behavioral therapy for insomnia in a heterogenous study sample: results from a randomized controlled trial. SLEEP, 2023, 46, 1–14

10 Leonie Franziska Maurer, Pauline Bauermann, Lena Karner, Charlotte Müller, Noah Lorenz, Annika Gieselmann. Investigating the efficacy of digital cognitive behavioural therapy in comparison to a sleep-monitoring application via integrated diary and actigraphy: A randomised–controlled trial. J Sleep Res. 2024;e14255.

11 Charles M. Morin. Profile of Somryst Prescription Digital Therapeutic for Chronic Insomnia: Overview of Safety and Efficacy. Expert Review of Medical Devices, 2020, Vol. 17, No. 12, 1239–1248

12 Isa Okajima, Yoko Komada, Yuichi Inoue. A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia. Sleep and Biological Rhythms 2011;9:24–34

13 Hui Ling Soh, Roger C. Ho, Cyrus S. Ho, Wilson W. Tam. Efficacy of digital cognitive behavioural therapy for insomnia: a meta-analysis of randomised controlled trials. Sleep Medicine 75 (2020) 315e325

14 National Federation of Health Insurance Societies. Investigative Research on Receipt Analysis Contributing to Policy Making III. [in Japanese] Comprehensive Medical Security Policy Survey and Research Grant Project, October 2017.

15 De Crescenzo F, D’Alò GL, Ostinelli EG, Ciabattini M, Di Franco V, Watanabe N, Kurtulmus A, Tomlinson A, Mitrova Z, Foti F, Del Giovane C, Quested DJ, Cowen PJ, Barbui C, Amato L, Efthimiou O, Cipriani A., Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults- a systematic review and network meta-analysis, Lancet 2022; 400: 170–84

16 Package insert (Rozerem Tablets) [in Japanese] revised in November 2023 (second edition)

17 Package insert (Dayvigo Tablets) [in Japanese] revised in December 2024 (third edition)

18 Package insert (Quviviq Tablets) [in Japanese] revised in December 2024 (third edition)