December 19, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health 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 (newly created)
Brand Name	SUSMED Digital Therapeutic App for Insomnia Med CBT-i
Applicant	Susmed, Inc.
Date of Application	February 1, 2022 (Application for marketing approval)

Results of Deliberation

In its meeting held on December 19, 2022, 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 Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

The period of survey for the use-results evaluation (use-results survey) should be 3 years and 11 months. The product should be approved with the following conditions.

Approval Conditions

The applicant is required to take necessary actions, such as disseminating the proper-use guidelines prepared in cooperation with the relevant academic societies and providing training programs, to ensure that the product is used only by physicians with sufficient knowledge of insomnia who have acquired thorough knowledge of cognitive behavioral therapy for insomnia (CBT-I) and the CBT-I program provided by the product.

The brand name of the product should be changed to “SUSMED Med CBT-i App for Insomnia.” The intended use or indication should be changed to “To provide support for cognitive behavioral therapy performed by the physician in the treatment of insomnia.”

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Review Report

December 1, 2022
Pharmaceuticals and Medical Devices Agency

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

Classification	Program 2, Software for treatment of diseases
Term Name	Insomnia treatment software (to be newly created)
Brand Name	SUSMED Digital Therapeutic App for Insomnia Med CBT-i
Applicant	Susmed, Inc.
Date of Application	February 1, 2022
Reviewing Office	Office of Software as a Medical Device

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Review Results

December 1, 2022

Classification	Program 2, Software for treatment of diseases
Term Name	Insomnia treatment software (to be newly created)
Brand Name	SUSMED Digital Therapeutic App for Insomnia Med CBT-i
Applicant	Susmed, Inc.
Date of Application	February 1, 2022

Results of Review

The "SUSMED Digital Therapeutic App for Insomnia Med CBT-i" (hereinafter referred to as "SUSMED App") is application software installed on mobile devices and used for cognitive behavioral therapy for insomnia (CBT-I). The CBT-I with SUSMED App is structured with "sleep hygiene education," "sleep log (sleep diary)," "sleep restriction therapy," "stimulus control therapy," and "cognitive therapy" components. Other features of SUSMED App include the sleepiness test. Patients treated with SUSMED App receive sleep hygiene education and fill out sleep logs for 7 days. Thereafter, they receive CBT-I for 8 weeks, during which they assess their insomnia status using the Athens Insomnia Scale (AIS)[i] and set the target bedtime and rising time (i.e., time to get into and out of bed) once a week. The applicant submitted non-clinical data on SUSMED App, i.e., performance data and data summarizing the progress of the software development life cycle process. There was no particular problem in the submitted data.

The applicant submitted the results of the following clinical studies conducted in Japan: Study SYK01 (exploratory study), Study SYK02 (pivotal clinical study), and Study SY01 (clinical study of the predecessor product).

The pivotal clinical study was a sham-controlled, multi-center, dynamic allocation, parallel-group double-blind study. It was conducted at 9 study centers in Japan in patients aged ≥20 years who were diagnosed with insomnia according to ICSD-3[ii] and required treatment. The results of the

[i] A self-assessment scale for insomnia with the maximum score of 24. The results are classified into "no problem" (scores of 1 to 3), "slightly suspected insomnia" (scores of 4 to 5), and "likely to be insomnia" (scores of ≥6).
[ii] International Classification of Sleep Disorders, third edition.

primary endpoint, the change in AIS (mean ± standard deviation [SD]) from baseline to Week 8, was −6.7 ± 4.4 in the active group and −3.3 ± 4.0 in the sham group. The difference in the mean change in AIS between the active and sham groups was −3.4 ($P < 0.001$), demonstrating the superiority of SUSMED App over the sham. The following secondary endpoints were evaluated:

- The change in AIS, item-by-item, from baseline to Week 8
- The change from baseline in Clinical Global Impressions-Improvement (CGI-I)[iii]
- The proportion of patients with AIS of <6 points at Week 8
- Necessity of medication at the end of study
- The change from baseline in sleep onset latency, sleep efficiency, and the number of nocturnal awakenings based on the sleep logs and actigraph data.

The results demonstrated the superiority of SUSMED App over the sham in the secondary endpoints, except for awakening-related endpoints (an AIS item "awakenings during the night," and "the number of nocturnal awakenings" based on sleep logs and data from actigraph).

As for the safety assessment, neither the pivotal study nor the exploratory study reported any adverse events for which a causal relationship to SUSMED App could not be ruled out or any malfunctions leading to serious adverse events.

After evaluating the risk-benefit balance based on the efficacy and safety results from the pivotal and other clinical studies, PMDA has concluded that SUSMED App is clinically useful because currently many patients who should, or wish to, receive CBT-I do not have access to CBT-I due to the lack of its availability in clinical practice. The safety of SUSMED App in clinical practice should be continuously evaluated through a use-results survey or other means, and the applicant should take actions to ensure the proper use of SUSMED App as necessary.

In order to introduce SUSMED App, a highly novel product in the Japanese market, as a more effective and safer medical device, it is important to ensure that physicians well-versed in face-to-face CBT-I select eligible patients and properly use SUSMED App, as risk minimization activities. Therefore the proper use guidelines on SUSMED App should be prepared by the relevant academic societies as a post-marketing safety activity to ensure its proper use.

As a result of its review, PMDA has concluded that 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.

[iii] 1 = very much worse; 2 = much worse; 3 = minimally worse; 4 = unchanged; 5 = minimally improved; 6 = much improved; 7 = very much improved; 0 = not assessed

Intended Use

To perform cognitive behavioral therapy for the treatment of insomnia

Approval Conditions

The applicant is required to take necessary actions, such as disseminating the proper-use guidelines prepared in cooperation with the relevant academic societies and providing training programs, to ensure that the product is used only by physicians with sufficient knowledge of insomnia who have acquired thorough knowledge of cognitive behavioral therapy for insomnia (CBT-I) and the CBT-I program provided by the product.

Review Report

December 1, 2022

Product for Review

Classification	Program 2, Software for treatment of diseases
Term Name	Insomnia treatment software (to be newly created)
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Date of Application	February 1, 2022
Proposed Intended Use	Treatment of insomnia

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List of Abbreviations

AASM	American Academy of Sleep Medicine
ACP	American College of Physicians
AIS	Athens Insomnia Scale
BMI	Body Mass Index
CGI-I	Clinical Global Impressions-Improvement
CBT	Cognitive behavioral therapy
CBT-I	Cognitive behavioral therapy for insomnia
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
NICE	National institute for Health and Clinical Excellence
QIDS	Quick Inventory of Depressive Symptomatology
WHO	World Health Organization

I. Product Overview

The “SUSMED Digital Therapeutic App for Insomnia Med CBT-i” (hereinafter referred to as “SUSMED App”) is application software installed on mobile devices and used for providing cognitive behavioral therapy for insomnia (CBT-I).

Cognitive behavioral therapy is a psychological treatment that focuses on changing cognition and thought patterns of patients in order to make them feel at ease. While CBT has a wide range of clinical applications in psychiatry, such as depression and anxiety disorder, CBT-I has been used in patients with insomnia. The cause/mechanism factors of insomnia consist of (a) the predisposing factors (e.g., methodical personality, age), (b) precipitating factors (e.g., studying for entrance exams, heavy workload), and (3) perpetuating factors (a condition in which a patient becomes unintentionally anxious when getting into bed, and sleeplessness causes stress, making it more difficult to go to sleep). CBT-I addresses insomnia by focusing on the perpetuating factors, alleviating somatized tension and learned sleep-preventing associations, thereby improving insomnia symptoms.[1]

A published report[2] states that CBT-I is classified into sleep hygiene education, sleep diary, stimulus control therapy, sleep restriction therapy, cognitive therapy, and relaxation (Table 1). The sleep scheduling technique, a combination of stimulus control therapy and sleep restriction therapy, restricts time in bed in a well-ordered manner, thereby regulating the circadian rhythm (biological rhythm that repeats in roughly 24-hour cycles) and homeostasis (maintenance of a constant internal environment in the body) to increase sleep pressure (need and desire to sleep). Furthermore, sleep scheduling is a treatment technique intended to eliminate the conditioned arousal: “bed equals awakening,” i.e., erroneous beliefs that bed is a place to be awake, thereby improving sleep quality, and is regarded as the core technique of CBT-I.[3]

Table 1. Components of CBT-I[4]

Sleep hygiene education		Provide patients with accurate information on sleep hygiene to promote lifestyle practices for quality sleep. Details of sleep hygiene education: ■ Sleeping time required ■ Morning sunlight exposure ■ Diet (avoid increased calorie intake at night) ■ Sleeping and exercise (increasing core body temperature by exercise, taking a warm [not hot] bath, avoiding doing exercise or taking a bath immediately before bedtime) ■ Avoid stimulants such as caffeine, tobacco, and alcohol as these make it more difficult to fall asleep ■ Creating the right sleep environment (keep the room dark and quiet; avoid staring at the LED display of a TV, personal computer, and smart phone) ■ Relaxation before going to bed ■ How to spend time on weekends and holidays, nap (get out of bed in the morning at a regular time on weekends and holidays, limit the nap to <30 minutes)
Sleep diary		Record the time when the patient got into bed, fell asleep, had nocturnal awakening(s), woke up, got out of bed, and had a nap/dozing off, etc.
Sleep scheduling	Stimulus control therapy	A technique to alleviate sleep-preventing associations and somatized tension by eliminating stimuli undesirable for sleep and by creating a conditioned association between bedroom and sleep. The technique is summarized below. Details of stimulus control therapy: ■ Lie down on the bed only when sleepy. ■ Avoid using the bed for activities other than sleep or sex. Do not watch TV or eat in the bedroom. ■ Leave the bed if unable to sleep for ≥20 minutes and return to bed when sleepy. ■ Get out of bed at the same time every morning even after failing to fall asleep the night before. ■ Avoid napping throughout the day.
	Sleep restriction therapy	Limit the patient's time in bed such that it is equal to the sleep duration estimated based on the sleep diaries. When the patient was able to sleep ≥85% of the duration for 5 consecutive days, increase the time in bed by 15 minutes.
Cognitive therapy		Reduce anxiety and excessive awareness about sleeplessness, and change wrong thoughts (dysfunctional beliefs) about sleep.
Relaxation		There are various relaxation therapies to improve insomnia, such as not only progressive muscle relaxation but also mindfulness, deep breathing, music, aromatherapy, light reading, and spending time with pets. Patients should find a practicable relaxation method suitable for themselves and continue to practice it.

The CBT-I with SUSMED App consists of “sleep hygiene education,” “sleep log (sleep diary),” “sleep restriction therapy,” “stimulus control therapy,” and “cognitive therapy.” Other features of SUSMED App include the insomnia scale assessment and sleepiness test. As shown in Figure 1 and Table 2, patients treated with SUSMED App do the following:

- Receive sleep hygiene education and fill out sleep logs for 7 days
- Perform reviews every morning and evening for 8 weeks
- Complete the Athens Insomnia Scale (AIS) questionnaire (Table 3) to assess insomnia status and set the target bedtime and rising time once a week.

After 9 weeks of treatment with SUSMED App, data entry in the app such as for reviews is automatically disabled, and when the app is started, it displays a message that the treatment period has ended. In addition, to prevent SUSMED App from being a trigger for the use of the patient’s smart phone in bed, the app is designed so that patients cannot enter or check data while they are in bed (i.e., from bedtime at night through rising time). Normally, data entered by patients are stored in the database of the management system.

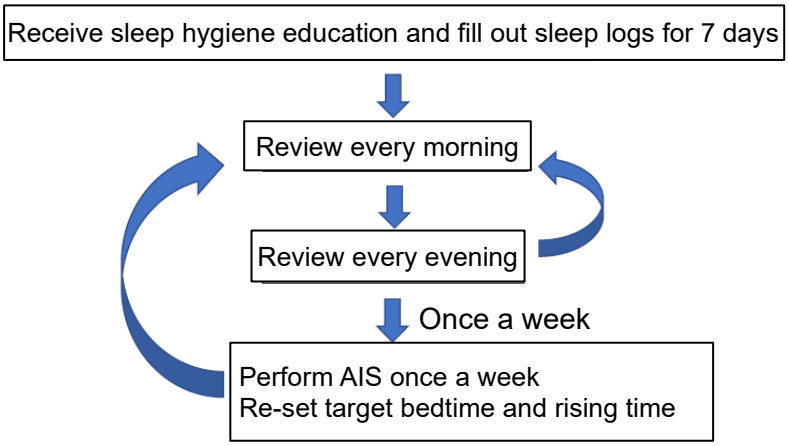


Figure 1. Eight weeks of CBT-I using SUSMED App

Table 2. Main features of SUSMED App

Sleep hygiene education

Timing	Features of SUSMED App
Review in the morning	[redacted]

Sleep log

Timing	Features of SUSMED App
Review in the morning	[redacted]

Sleep restriction therapy

Timing	Features of SUSMED App
Once a week	[redacted] The time in bed (from bedtime at night through rising time) is adjusted according to the sleep efficiency calculated from the sleep log, daytime sleepiness, and the status of adherence to the target bedtime. [redacted]

	[redacted]
Review in the evening	[redacted]

[iv] Immediate sleepiness scale. 1 = extremely alert, 2 = very alert, 3 = alert, 4 = rather alert, 5 = neither alert nor sleepy, 6 = some signs of sleepiness, 7 = sleepy (but no effort to keep awake), 8 = sleepy (some effort to keep awake), 9 = very sleepy (great effort keeping awake, fighting sleep).

Stimulus control therapy

Timing	Features of SUSMED App
Review in the morning	[redacted]
Review in the evening	[redacted]

Timing	Features of SUSMED App
	[redacted]

Cognitive therapy

Timing	Features of SUSMED App
Review in the evening	Cognitive therapy is conducted by visualizing the patient's anxieties and thoughts with the following steps: [redacted]

Insomnia scale assessment

Timing	Features of SUSMED App
Once a week	The patient's insomnia is self-assessed by AIS

Sleepiness test

Timing	Feature of SUSMED App
Review in the evening	Sleepiness is checked by [redacted].

Table 3. Self-assessment of insomnia by Athens Insomnia Scale (AIS)

Check the items that occurred at least 3 times a week during the past 1 month.

1	Did it take time to fall asleep after getting into bed?	0	Better than usual
		1	Slightly longer than usual
		2	Markedly longer than usual
		3	Much longer than usual or did not sleep at all
2	Did you wake up during the night?	0	No problem
		1	Minor problem
		2	Considerable problem
		3	Serious problem or did not sleep at all
3	Was your final awakening earlier than desired and were you unable to fall back to sleep?	0	No
		1	A little earlier
		2	Markedly earlier
		3	Much earlier or did not sleep at all
4	Was the total sleep duration (nighttime sleep and nap) sufficient?	0	Sufficient
		1	Slightly insufficient
		2	Markedly insufficient
		3	Very insufficient or did not sleep at all
5	How do you feel about the overall quality of sleep?	0	Satisfactory
		1	Slightly unsatisfactory
		2	Markedly unsatisfactory
		3	Very unsatisfactory or did not sleep at all
6	How was your sense of well-being during the day?	0	Normal
		1	Slightly decreased
		2	Markedly decreased
		3	Very decreased
7	How was physical and mental functioning during the day?	0	Normal
		1	Slightly decreased
		2	Markedly decreased
		3	Very decreased
8	Did you feel sleepy during the day?	0	None
		1	Mild
		2	Considerable
		3	Intense
	Total		1-3 points: No sleep disturbance 4-5 points: Suspected insomnia ≥6 points: Highly likely to have insomnia

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 SUSMED App declared that they did not fall under the Item 5 of the Rules for Convening Expert Discussions, etc. by

Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

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

1.(1) History of development

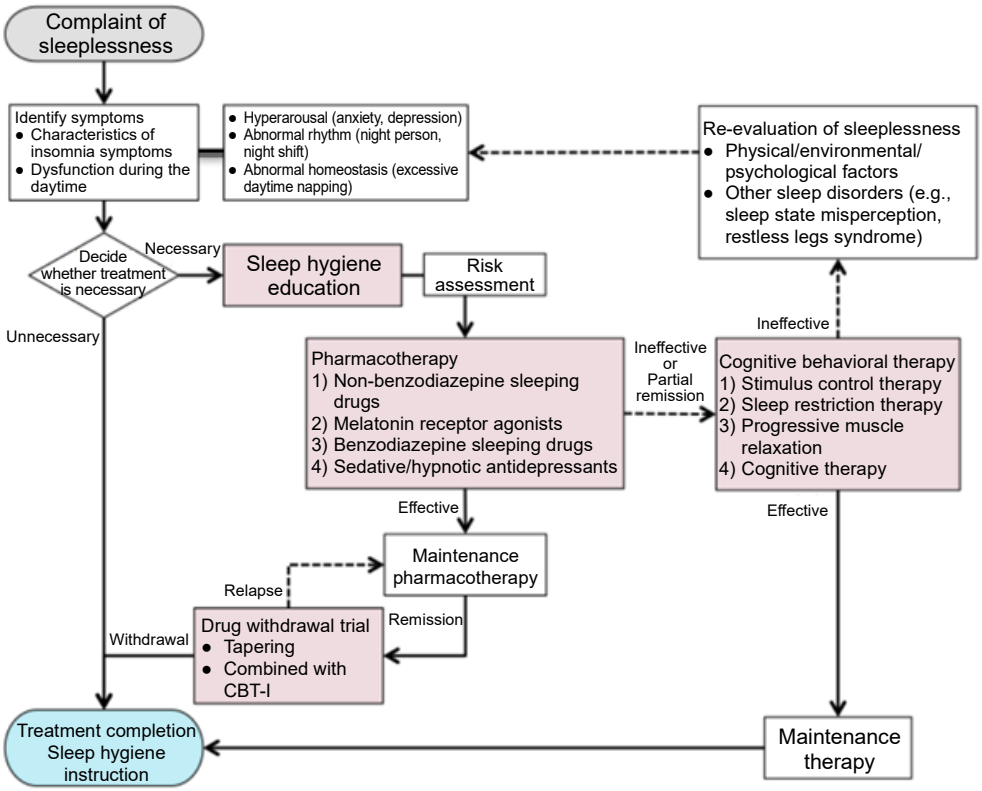
1.(1).A Summary of the data submitted

Insomnia is a form of sleep disorder characterized by symptoms including difficulty initiating sleep (sleep onset insomnia), shallow sleep and frequent awakenings during the night (nocturnal awakenings), awakening earlier than desired and unable to fall back to sleep (early morning awakening), and unrefreshing sleep (nonrestorative sleep). The diagnostic criteria for insomnia are presented in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) and International Classification of Sleep Disorders, third edition (ICSD-3)[5] (Table 4). The preceding editions of DSM and ICSD distinguished between "primary insomnia" and "secondary insomnia," which is a sleep disorder associated with other diseases. DSM-5 and ICSD-3, however, state that insomnia should be diagnosed without distinction between primary and secondary insomnia.

Table 4. Diagnostic criteria for insomnia in the International Classification of Sleep Disorders, third edition

Criteria A-E must be met.
A. The patient reports, or the patient's parent or caregiver observes, one or more of the following:
1. Difficulty initiating sleep
2. Difficulty maintaining sleep
3. Waking up earlier than desired
4. Resistance to going to bed on appropriate schedule
5. Difficulty sleeping without parent or caregiver intervention
B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty:
1. Fatigue/malaise
2. Attention, concentration or memory impairment
3. Impaired social, family, occupational or academic performance
4. Mood disturbance/irritability
5. Daytime sleepiness
6. Behavioral problems (e.g. hyperactivity, impulsivity, aggression)
7. Reduced motivation/energy/initiative
8. Proneness for errors/accidents
9. Concerns about or dissatisfaction with sleep
C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e. enough time is allotted for sleep) or inadequate circumstances (i.e. the environment is safe, dark, quiet and comfortable) for sleep.
D. Short-term insomnia, the sleep disturbance and associated daytime symptoms have been present for <3 months; chronic insomnia, the sleep disturbance and associated daytime symptoms occur at least three times per week and for at least 3 months.
E. The sleep/wake difficulty is not explained more clearly by another sleep disorder.

The prevalence of sleep onset insomnia in Japan is 8.3% of the population, which accounts for 21.4% of total insomnia.[6] According to the summary of the National Health and Nutrition Survey 2018, the proportion of people without adequ0ate rest from sleep was 21.7%, indicating a significant increase from 2009. As shown in Figure 2, information on the treatment for insomnia is outlined in the Clinical Guidelines for Proper Use and Withdrawal of Hypnotics: Manual for Insomnia Treatment With an Exit Plan[7] (hereinafter referred to as "the Japanese Clinical Guidelines"). Sleep hygiene education, pharmacotherapy, CBT-I, and other therapies have been performed according to the patient's symptoms. Currently, treatment approaches widely used in Japan are pharmacotherapies with sleeping drugs. One of the advantages of these drugs is that they work immediately to reduce sleep onset latency, improve nocturnal awakening, and other conditions. Conversely, sleeping drugs have problems, namely adverse reactions including physical symptoms such as dizziness and falls, carry-over effects such as headache and malaise, and drug interactions with concomitant medications. Furthermore, rebound insomnia and withdrawal symptoms after stopping taking sleeping drugs may lead to drug dependence; therefore, the use of sleeping drugs should be limited to the minimum necessary.



The Japanese Clinical Guidelines

Section 4. Treatment algorithm, (6) Cognitive behavioral therapy

Psychological/behavioral interventions should also be initiated concurrently with pharmacotherapy as early as possible, as far as the situation permits. A representative intervention is CBT-I. The Japanese Clinical Guidelines state, "CBT-I is defined as a second-line treatment for patients with insomnia not adequately responding to pharmacotherapy, but CBT-I is also effective as a first-line treatment or in combination with pharmacotherapy."

Figure 2. Treatment algorithm

CBT-I is usually delivered through face-to-face sessions (face-to-face CBT-I) with a total of 4 to 6 sessions, each lasting 50 minutes. At the end of each meeting, homework is assigned, due for the next meeting, and the status of a patient's engagement with homework is to be checked at the next meeting.[8] In many cases, a follow-up session is conducted several months after the completion of face-to-face CBT-I sessions to check the maintenance effect of CBT-I.

There have been reports that 50% of patients treated with CBT-I achieved remission,[3,9] 70% to 80% of patients treated with CBT-I are expected to have improvements in symptoms,[10] and there are other reports on the efficacy of CBT-I. The Clinical Practice Guideline from the American

College of Physicians [11] summarizes the efficacy and evidence levels of CBT-I and pharmacotherapy. According to this guideline, the efficacy and the evidence level of pharmacotherapy vary from drug to drug, but the efficacy of CBT-I is roughly equivalent to that of pharmacotherapy in terms of remission, treatment response, subjective insomnia scales, sleep onset latency, duration of nocturnal awakenings, and other indices, while the evidence level of CBT-I tends to be higher than that of pharmacotherapy. Furthermore, CBT-I is known to maintain treatment effect over a longer period: results of meta-analyses have shown that improvements were sustained at 6 months or 12 months after treatment completion,[9,10] while the results of another study indicated that the quantity of sleeping drugs was reduced.[12] A study that compared the long-term effects of CBT-I and sleeping drugs showed that the duration of awakenings after sleep onset remained improved in patients receiving CBT-I group even at 2 years after treatment, but the symptoms of patients receiving sleeping drugs gradually returned to pretreatment status from 3 months, 1 year, to 2 years post-treatment.[13] The guidelines published by the American Academy of Sleep Medicine (AASM) and European guidelines[14,15] recommend CBT-I, which does not depend on medications, as the first-line treatment for insomnia. The guidelines published by the National Institute for Health and Care Excellence (NICE) of the UK recommend treatment for insomnia with a digital app as an option to replace pharmacotherapy.

In Japan (in the treatment algorithm of the Japanese Clinical Guidelines), CBT-I is defined as a second-line treatment for patients not responding adequately to pharmacotherapy. However, the Japanese Clinical Guidelines also recommend that psychological/behavioral interventions (e.g., cognitive behavioral therapy for insomnia) should also be initiated concurrently with pharmacotherapy as early as possible, as far as the situation permits, and state that CBT-I is also effective as a first-line treatment or in combination with pharmacotherapy. Meanwhile, CBT-I has not been widely available because of a shortage in healthcare staff and for other reasons. Consequently, the amount of sleeping drugs prescribed per capita in Japan is exceptionally high among developed countries, as much as 6-fold higher than in the US.[16]

In such circumstances, where there is an excessive overdependence on sleeping drugs in the treatment of insomnia in Japan, the applicant developed SUSMED App to provide CBT-I, which makes use of information and communication technology, thereby enabling insomnia treatment with decreased dependence on pharmacotherapy. Based on the data described later in Section "6.A.(3) Clinical study of the predecessor app," for SUSMED App, [redacted]

1.(2) Use in foreign countries

SUSMED App has not been approved or licensed in foreign countries.

2. Design and Development

2.(1) Performance and safety specifications

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

The proposed performance specifications of SUSMED App include a series of functions to be used in treatment as shown in Table 2.

- Interview function (review function)
- Treatment function (sleep hygiene education, stimulus control therapy, sleep restriction therapy, sleepiness test, cognitive therapy, and insomnia scale assessment)
- Check function (sleep log, detailed information on daily basis)
- Control function (SUSMED App cannot be used during a certain time of day)

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

PMDA reviewed the data related to the specifications, and concluded that there were no problems in the items, test methods and acceptance criteria.

2.(2) Safety specifications

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

The applicant submitted data summarizing the implementation status of life cycle processes required for safety design and maintenance of SUSMED App in accordance with JIS T 2304:2017 "Medical device software–Software life cycle processes."

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

PMDA comprehensively reviewed the submitted data taking into account the discussion presented later in Section "3.B Outline of the review conducted by PMDA," and concluded that there were no particular problems.

2.(3) Performance

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

The applicant submitted data related to the performance of SUSMED App, i.e., data that evaluated whether each function operates properly.

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

PMDA reviewed the submitted data, which had been evaluated by the applicant for proper operation of the functions, and concluded that there were 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 declaring that 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 Ministerial Announcement No. 122, 2005).

3.B Outline of the review conducted by PMDA

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

(1) The conformity of 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 described later in Section "6.B Outline of the review conducted by PMDA," to ensure its efficacy and safety, SUSMED App should be used by appropriate physicians in accordance with the appropriate clinical positioning. For this reason, PMDA decided to impose an approval condition to the following effect: Proper use guidelines for SUSMED App should be prepared by the relevant academic societies and the guidelines should be followed when using SUSMED App.

(2) The conformity of SUSMED App to Article 2, which stipulates risk management throughout the life cycle of medical devices.

PMDA's view:

As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," safety information should be gathered in post-marketing settings, for the following reasons:

(a) Face-to-face CBT-I is not widely available in Japan. Under this circumstance, adverse events and other safety issues associated with the use of SUSMED App should be evaluated.

(b) Safety and other information of patients who were excluded from the clinical studies should be evaluated.
(c) Long-term safety and efficacy should be evaluated.

PMDA instructed the applicant to conduct a use-results survey.

(3) The conformity of SUSMED App to Article 3, which stipulates the performance and function of medical devices, and to Article 6, which stipulates the efficacy of medical devices:

PMDA's view:
As described later in Sections "6.B Outline of the review conducted by PMDA," the pivotal clinical study demonstrated a certain level of clinically meaningful improvements in insomnia symptoms in patients treated with SUSMED App. There was no problem with the conformity of SUSMED App to Articles 3 and 6.

(4) The conformity of SUSMED App to Article 12, which stipulates requirements that must be considered in relation to the development life cycle of program-driven medical devices:

PMDA's view:
As described earlier in Sections "2.(1).B Outline of the review conducted by PMDA" and "2.(2).B. Outline of the review conducted by PMDA," assessment showed that requirements related to the software life cycle process are appropriately addressed and SUSMED App operates properly. Thus, there was no problem with the conformity of SUSMED App to Article 12.

(5) The conformity of SUSMED App to Article 17, which stipulates the general requirements for disseminating information to users by publishing Information on Precautions, etc. and by including the information in the instructions for use, etc.

PMDA's view:
As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," in order to maintain its risk-benefit balance, it is critical for prescribing physicians to select eligible patients for SUSMED App and to use it properly after becoming familiar with CBT-I and the features of SUSMED App. Therefore, relevant information should be disseminated through the Information on Precautions, etc., proper use guidelines, and by other means.

Based on the above, PMDA comprehensively reviewed the conformity of 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, risk management system, and its progress in accordance with JIS T 14971:2012 "Medical devices–Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA reviewed the risk management data as shown below.

The SUSMED App operates on the patient's own mobile device, and the management system for the primary care physicians to monitor the status of app use and other data operates on web browsers. PMDA asked the applicant to explain measures to ensure cybersecurity.

The applicant's explanation:

The applicant performed an evaluation in terms of requirements for ensuring cybersecurity in accordance with "Guidance on Ensuring Cyber Security of Medical Devices" (PSEHB/MDED Notification No. 0724-1 and PSEHB/PSD Notification No. 0724-1, dated July 24, 2018).

[redacted]

[redacted]

[redacted]

As a result of the above measures, cyber risks have been reduced to the greatest possible extent, and the results were confirmed to be acceptable.

Based on the applicant's explanation about ensuring cybersecurity, as well as the abovementioned issues discussed in Section "3.B Outline of the review conducted by PMDA," PMDA comprehensively reviewed the risk management data, and concluded that there were no particular problems.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant did not submit data on the manufacturing process of SUSMED App in accordance with the Notification "Handling of Medical Device Software" (PFSB/MDRMPE Notification No. 1121-33, PFSB/SD Notification No. 1121-1, and PFSB/CND Notification No. 1121-29, dated on November 21, 2014).

5.B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with omitting, in accordance with the above notifications, the submission of data on the manufacturing process of SUSMED App.

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

6.A Summary of the data submitted

For the clinical evaluation of SUSMED App, the applicant submitted data from the following clinical studies conducted in Japan: Study SYK01 (exploratory study), Study SYK02 (pivotal clinical study), and Study SY01 (clinical study of the predecessor product). The following sections mainly discuss the data from the clinical studies.

6.A.(1) Pivotal clinical study (Study period, March 5, 2021 to September 17, 2021)

The pivotal clinical study was conducted in Japan as a sham-controlled, multi-center, dynamic allocation, parallel-group double-blind study to evaluate the efficacy and safety of SUSMED App in patients aged ≥20 years who were diagnosed with insomnia according to ICSD-3 and required treatment (Table 5). The primary endpoint was the change in AIS from baseline to Week 8. The study had 2 groups: (a) the active group, in which patients were treated with CBT-I using SUSMED App, and (b) the sham group, in which patients used a sham app (Table 6). The study tested the superiority of SUSMED App over the sham app. The patients received sleep hygiene education for 1 week after the date of consent. Patients with an AIS score of <9 points, and those who did not require sleep improvements (i.e., sleep efficiency of ≥85% based on the sleep log; or

sleep onset latency of <1 hour) were excluded. The remaining patients were allocated to the active and sham groups at a ratio of 1:1, resulting in a total enrollment of 175 patients (87 in the active group and 88 in the sham group).

Table 5. Outline of the pivotal clinical study

Category	Details
Study objective	To evaluate the efficacy of SUSMED App at Week 8 based on the change in AIS from baseline (the primary endpoint) versus the sham app.
Type of study	Sham-controlled, multi-center, dynamic allocation, parallel-group double-blind study
Study population	Patients with insomnia
Inclusion criteria	(1) Patients diagnosed with insomnia according to ICSD-3 who require treatment (2) Patients who have not responded adequately to the treatment of 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 SUSMED App (7) Patients who are able to install 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 provided a written consent to participate in the study
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 sleeping drugs (including antidepressants, anti-anxiety drugs) to treat insomnia symptoms (3) Patients who are taking, or have taken within 14 days prior to enrollment, sleeping drugs to treat insomnia symptoms (including ultrashort-acting, short-acting, and intermediate-acting sleeping drugs, and over-the-counter sleep aid drugs), antidepressants, anti-anxiety drugs, herbal medicines (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) (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 under treatment with medication (including Alzheimer's disease, Parkinson's disease, and epilepsy)

Category	Details
	(6) Patients with diagnosed or suspected (according to interview) sleep-related breathing disorders as a comorbidity who stop breathing during sleep or snore loudly in addition to excessive daytime sleepiness (7) Patients with diagnosed or suspected (according to interview) sleep-related movement disorders (e.g., restless legs syndrome, periodic limb movement disorder) as a comorbidity who have sleep-related sensations/motor symptoms such as abnormal sensations/movements at night (8) Patients with diagnosed or suspected (according to interview) central hypersomnia (e.g., narcolepsy) as a comorbidity who have excessive daytime sleepiness despite adequate sleep (9) Patients with diagnosed or suspected (according to interview) parasomnia (e.g., rapid eye movement sleep behaviour disorder) as a comorbidity who have abnormal behavior during sleep such as loud vocalization, limb movement, and walking (10) Patients with diagnosed or suspected (according to interview) circadian rhythm disorders (e.g., delayed sleep-phase syndrome) as a comorbidity who have irregular sleep-wake rhythm such as day-night reversal (11) Patients with a history, or a comorbidity, of alcohol dependence or drug addiction (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) (13) Pregnant or possibly pregnant or lactating women (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 (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 (16) Patients who received sleep hygiene education within the past 6 months or received cognitive behavioral therapy for insomnia symptoms in the past (17) Patients who have used SUSMED App or its prototype apps for clinical trials (Yawn, Yue) in the past (18) Patients who have used other study drugs or medical devices under development within the past 90 days (19) Patients who are considered to be ineligible by the investigator or subinvestigator
Sample size	175 patients
Method of use	The study device (app) was downloaded on the patient's smart phone and the app program was used for 56 days.
Testing/monitoring items and time frame	Primary efficacy endpoint: The change in AIS from baseline to Week 8 Secondary efficacy endpoints: (1) Change in AIS, item-by-item, from baseline to Week 8

Category	Details
	(2) Change in the Clinical Global Impressions-Improvement (CGI-I)[v] scale 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
Duration of use	57 days
Follow-up period	78 days
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: • Sleeping drugs (including drugs indicated for insomnia or sleep disorders) • Over-the-counter sleep aid drugs • 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 with a physician's prescription. The use of over-the-counter drugs at the patient's discretion was not allowed.)

[v] 1 = Very much worse; 2 = Much worse; 3 = Minimally worse; 4 = Unchanged; 5 = Minimally improved; 6 = Much improved; 7 = Very much improved; 0 = Not assessed

Category	Details
	(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.
Study period	71 days (See Figure 3)
Number of study centers	9 study centers

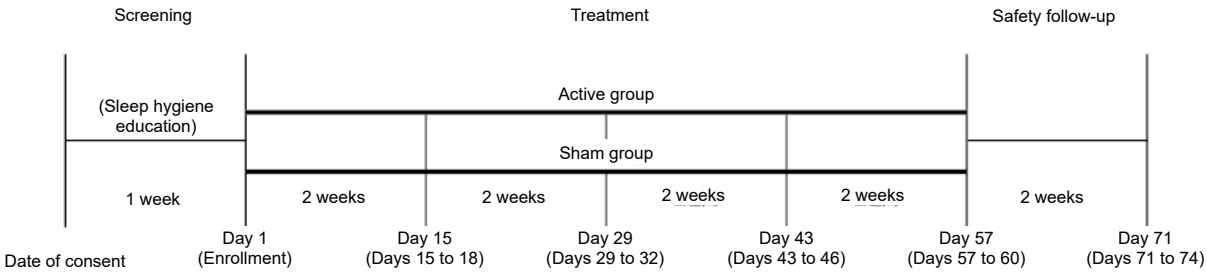


Figure 3. Study period

Table 6. Comparison of features of SUSMED App and sham app

Feature	Details	Sham	SUSMED App
Log in	Controlled so that only specified patients can use the app.	✓	✓
Terms of use	After logging in to SUSMED App, the terms of use screen will be displayed. If the user agrees to all the terms after reading them, the system allows the user to move to the initial set-up page.	✓	✓
Entry of patient characteristics data	[redacted]	✓	✓
Entry of target bedtime and target rising time	[redacted] Set the determined target bedtime and target rising time in the app.	✓	✓
AIS assessment	The AIS check page shows 8 questions to check the level of sleeplessness.[redacted]	✓	✓
Contact	The contact page shows contact information for users. [redacted]	✓	✓
Tutorial	To show how to use the app, a part of the content of SUSMED App is displayed as a tutorial and each feature is explained.	✓	✓
Push notification	Push notification is displayed to send the user messages from the app. [redacted]	✓	✓

Feature	Details	Sham	SUSMED App
Use discontinuation dialog	[redacted]	✓	✓
Sleep log	See Table 2	None	✓
Sleep hygiene education	See Table 2	None	✓
Stimulus control therapy	See Table 2	None	✓
Sleep restriction therapy	See Table 2	None	✓
Sleepiness test	See Table 2	None	✓
Cognitive therapy	See Table 2	None	✓

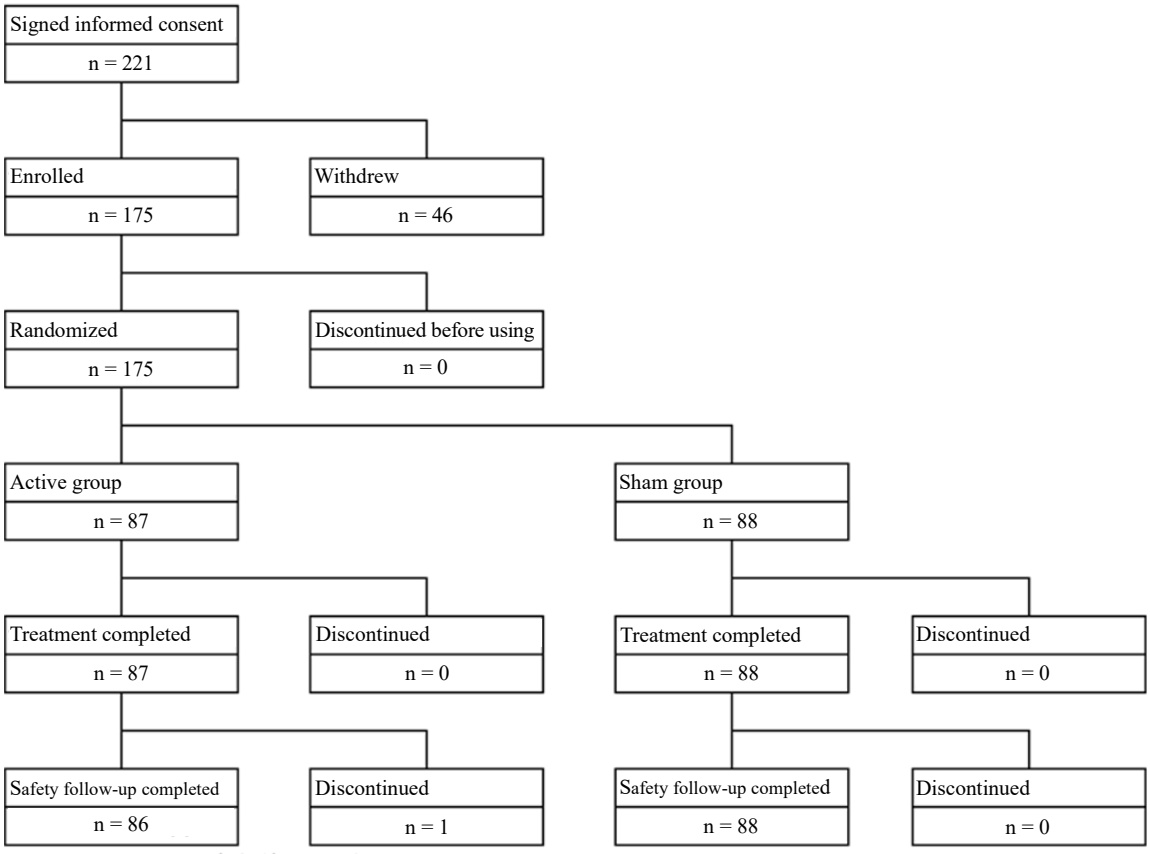


Figure 4. Disposition of patients

6.A.(1).1) Characteristics of patients

Table 7 shows the characteristics of patients enrolled in the pivotal clinical study.

Table 7. Patient characteristics

		Active	Sham
N		87	88
Age	Mean ± SD	42.4 ± 13.5	45.9 ± 13.2
	Median [Min, Max]	44 [21, 72]	46 [21, 78]
Age group	≥20 years and <40 years	41	35
	≥40 years and <65 years	40	45
	≥65 years	6	8
Sex	Male/female	32/55	41/47
BMI (kg/m^2)	Mean ± SD	22.7 ± 4.8	22.4 ± 3.7
	Median [Min, Max]	22.0 [16.0, 50.2]	21.7 [16.2, 38.8]
Prior medical history or comorbidity	Yes	26	26
	No	61	62
Prior use of medications	Yes	0	0
	No	87	88
Concomitant medications	Yes	26	31
	No	61	57
Concomitant therapies	Yes	0	0
	No	87	88
Baseline AIS	Mean ± SD	13.4 ± 2.8	13.6 ± 2.9
	Median [Min, Max]	13 [9, 21]	13 [9, 24]

6.A.(1).2) Study results

6.A.(1).2).(a) Efficacy endpoints

Table 8 shows the results of the primary endpoint and Table 9 shows the time course of AIS.

The change in AIS (mean ± SD) from baseline to Week 8, the primary endpoint, was −6.7 ± 4.4 in the active group and −3.3 ± 4.0 in the sham group. The difference in mean change in AIS between the active and sham groups was −3.4 ($P < 0.001$), demonstrating the superiority of SUSMED App over the sham app.

Table 8. Change in AIS from baseline to Week 8

Group	N	Baseline	Week 8	Change from baseline					Difference from sham	
		Mean	Mean	Mean	Min	Median	Max	SD	Difference	*P*-value[1)]
Active	87	13.4	6.7	−6.7	−19	−7	6	4.4	−3.4	<0.001
Sham	88	13.6	10.4	−3.3	−12	−3	6	4.0		

1) Welch's t-test

Table 9. Time course of AIS

Time point	Group	N	Mean	Min	Median	Max	SD
Baseline	Active	87	13.4	9	13	21	2.8
	Sham	88	13.6	9	13	24	2.9
Week 1	Active	87	9.9	1	10	21	3.8
	Sham	88	11.8	3	12	23	3.7
Week 2	Active	87	9.6	0	9	21	3.8
	Sham	88	11.7	2	11	24	3.9
Week 3	Active	87	9.0	0	8	22	4.4
	Sham	88	11.3	1	11	23	4.1
Week 4	Active	87	8.4	0	8	23	4.2
	Sham	88	10.9	2	10.5	23	4.2
Week 5	Active	87	7.8	0	8	22	4.2
	Sham	88	10.9	1	10	23	4.3
Week 6	Active	87	7.6	0	8	22	4.5
	Sham	88	10.5	0	10	24	4.5
Week 7	Active	87	7.0	0	8	20	4.2
	Sham	88	10.8	0	10	24	4.7
Week 8	Active	87	6.7	0	7	22	4.5
	Sham	88	10.4	0	9	24	4.8
Week 10	Active	86	5.9	0	6	22	4.0
	Sham	88	9.7	0	9	23	4.9

The results of secondary endpoints (1) to (5) are shown in Tables 10 to 15.

The change from baseline in AIS (mean ± SD), item-by-item, was as follows (Table 10):

- Sleep induction (time required to fall asleep after going to bed): −1.1 ± 0.7 (active) and −0.6 ± 0.8 (sham) with a between-group difference of −0.5 ($P < 0.001$)
- Awakenings during the night: −0.7 ± 0.8 (active) and −0.4 ± 0.7 (sham) with a between-group difference of −0.3 ($P = 0.063$)
- Awakening earlier than desired and unable to fall back to sleep: −0.7 ± 0.8 (active) and −0.2 ± 0.7 (sham) with a between-group difference of −0.5 ($P < 0.001$)
- Total sleep duration: −0.8 ± 0.7 (active) and −0.5 ± 0.7 (sham) with a between-group difference of −0.3 ($P = 0.003$)
- Overall quality of sleep: −1.1 ± 0.8 (active) and −0.6 ± 0.7 (sham) with a between-group difference of −0.5 ($P < 0.001$)
- Sense of well-being during the day: −0.9 ± 0.9 (active) and −0.4 ± 0.8 (sham) with a between-group difference of −0.5 ($P < 0.001$)
- Physical and mental functioning capacity during the day: −0.7 ± 0.8 (active) and −0.3 ± 0.8 (sham) with a between-group difference of −0.4 ($P = 0.003$)
- Sleepiness during the day: −0.8 ± 0.7 (active) and −0.2 ± 0.6 (sham) with a between-group difference of −0.6 ($P < 0.001$)

Table 10. Change in AIS, item-by-item, from baseline to Week 8

	Group	N	Baseline	Week 8	Change from baseline					Difference from sham	
			Mean	Mean	Mean	Min	Median	Max	SD	Difference	*P*-value[1)]
Sleep induction	Active	87	1.9	0.9	−1.1	−3	−1	1	0.7	−0.5	<0.001
	Sham	88	2.0	1.4	−0.6	−3	−1	1	0.8		
Awakenings during the night	Active	87	1.4	0.7	−0.7	−2	−1	1	0.8	−0.3	0.063
	Sham	88	1.6	1.2	−0.4	−2	0	1	0.7		
Awakening earlier than desired and unable to fall back to sleep	Active	87	1.4	0.7	−0.7	−2	−1	2	0.8	−0.5	<0.001
	Sham	88	1.4	1.2	−0.2	−2	0	1	0.7		
Total sleep duration	Active	87	1.8	1.0	−0.8	−2	−1	1	0.7	−0.3	0.003
	Sham	88	1.9	1.4	−0.5	−2	0	1	0.7		
Overall quality of sleep	Active	87	2.0	1.0	−1.1	−3	−1	0	0.8	−0.5	<0.001
	Sham	88	2.0	1.4	−0.6	−2	−1	1	0.7		
Sense of well-being during the day	Active	87	1.6	0.8	−0.9	−3	−1	1	0.9	−0.5	<0.001
	Sham	88	1.7	1.3	−0.4	−2	0	1	0.8		
Physical and mental functioning capacity during the day	Active	87	1.4	0.7	−0.7	−3	−1	2	0.8	−0.4	0.003
	Sham	88	1.5	1.1	−0.3	−2	0	1	0.8		
Sleepiness during the day	Active	87	1.8	0.9	−0.8	−3	−1	1	0.7	−0.6	<0.001
	Sham	88	1.6	1.4	−0.2	−1	0	1	0.6		

1) Welch's t-test

The change in CGI-I (mean ± SD) from baseline to Week 8 was 1.3 ± 0.8 (active) and 0.7 ± 0.8 (sham), with a mean difference of 0.6 ($P < 0.001$) between the active and sham groups.

Table 11. Change in CGI-I from baseline to Week 8

Group	N	Baseline	Week 8	Change from baseline					Difference from sham	
		Mean	Mean	Mean	Min	Median	Max	SD	Difference	*P*-value[1)]
Active	87	4	5.3	1.3	0	1	3	0.8	0.6	<0.001
Sham	88	4	4.7	0.7	−1	0.5	3	0.8		

1) Welch's t-test

The proportion of patients with an AIS of <6 points at Week 8 or treatment discontinuation (no patients actually discontinued the treatment) was 37.9% (33 of 87 patients) in the active group and 10.2% (9 of 88 patients) in the sham group, with the difference from the sham group being 27.7 percentage points ($P < 0.001$).

Table 12. The proportion of patients with an AIS of <6 points at Week 8 or treatment discontinuation

Group	N	Patients with an AIS <6 points		Difference from sham (percentage points)	
		n	Proportion (%)	Difference	*P*-value[1)]
Active	87	33	37.9	27.7	<0.001
Sham	88	9	10.2		

1) Testing for the difference in population proportions

At the end of study or treatment discontinuation (no patients actually discontinued the treatment), 6 patients (7.0%) in the active group and 13 patients (14.8%) in the sham group were considered to require medications.

Table 13. Necessity of medications at the end of study or treatment discontinuation

Group	N	Not required		Required	
		n	Proportion (%)	n	Proportion (%)
Active	87	80	93.0	6	7.0
Sham	88	75	85.2	13	14.8

The change from baseline in the following parameters (mean ± SD) based on sleep logs (paper-based) was as follows:

- Sleep onset latency: −38.4 ± 36.3 minutes (active) and −22.7 ± 32.6 minutes (sham) with a between-group difference of −15.7 minutes ($P = 0.003$)
- Sleep efficiency: 10.4 ± 9.8% (active) and 5.8 ± 7.7% (sham) with a between-group difference of 4.6 percentage points ($P = 0.001$)
- The number of nocturnal awakenings: −0.3 ± 0.7 times (active) and −0.3 ± 0.8 times (sham) with a between-group difference of 0.0 ($P = 0.75$)

Table 14. Change from baseline in sleep onset latency, sleep efficiency, and the number of nocturnal awakenings based on sleep log

Group	N	Baseline	End	Change from baseline					Difference from sham	
		Mean	Mean	Mean	Min	Median	Max	SD	Difference	*P*-value[1)]
Sleep onset latency (min)										
Active	86	94.6	56.2	−38.4	−154.3	−34.3	64.3	36.3	−15.7	0.003
Sham	88	88.0	65.3	−22.7	−175.7	−17.1	51.4	32.6		
Sleep efficiency (%)										
Active	86	69.7	80.2	10.4	−35.3	11.5	34.6	9.8	4.6	0.001
Sham	88	71.6	77.4	5.8	−12.7	5.6	27.1	7.7		
Number of nocturnal awakenings (times)										
Active	86	1.3	1.0	−0.3	−2.0	−0.3	2.7	0.7	0.0	0.75
Sham	88	1.4	1.0	−0.3	−3.3	−0.1	1.6	0.8		

1) Welch's t-test

The change from baseline in the following parameters (mean ± SD) based on actigraph data was as follows:

- Sleep onset latency: −27.9 ± 30.1 minutes (active) and −17.1 ± 25.2 (sham) with a between-group difference of −10.8 minutes ($P = 0.020$)
- Sleep efficiency: 6.6 ± 8.0% (active) and 3.4 ± 7.7% (sham) with a between-group difference of 3.2 percentage points ($P = 0.015$)
- Nocturnal awakenings: 0.0 ± 6.5 (active) and 0.3 ± 5.3 (sham) with a between-group difference of −0.3 ($P = 0.746$)

Table 15. Change from baseline in sleep onset latency, sleep efficiency, and the number of nocturnal awakenings based on actigraph data

Group	N	Baseline	End	Change from baseline					Difference from sham	
		Mean	Mean	Mean	Min	Median	Max	SD	Difference	*P*-value[1)]
Sleep onset latency (min)										
Active	73	92.9	65.0	−27.9	−98.7	−27.0	34.1	30.1	−10.8	0.020
Sham	73	82.2	65.1	−17.1	−84.4	−15.4	39.6	25.2		
Sleep efficiency (%)										
Active	73	69.3	75.9	6.6	−14.5	6.7	23.1	8.0	3.2	0.015
Sham	73	72.4	75.8	3.4	−23.0	2.8	21.7	7.7		
Number of nocturnal awakenings (times)										
Active	73	23.6	23.6	0.0	−15.1	−0.1	12.0	6.5	−0.3	0.746
Sham	73	23.4	23.7	0.3	−12.9	0.0	15.4	5.3		

1) Welch's t-test

6.A.(1).2).(b) Safety endpoints

There were no adverse events for which a causal relationship to the study device could not be ruled out in either group. Pyrexia was the most frequent adverse event in both groups, with an incidence of 3.4% (3 of 87 patients) in the active group and 8.0% (7 of 88 patients) in the sham group. No malfunctions of SUSMED App were reported.

6.A.(2) Exploratory study (Study period, [redacted], 20[redacted] to [redacted], 20[redacted])

A sham-controlled, multi-center, dynamic-allocation, parallel-group, double-blind study was conducted in Japan to examine the design of the pivotal clinical study that was to be conducted to evaluate the efficacy and safety of SUSMED App (Table 16). The exploratory study was conducted in patients aged ≥20 years who were diagnosed with insomnia according to ICSD-3 and required treatment. The change in AIS from baseline to Week 8 in the group receiving CBT-I with SUSMED App (active group) was compared with that in the group using the sham app (sham group). The patients received sleep hygiene education for 1 week after the date of consent. Patients with an AIS score of <9 points, and those who did not require sleep improvements (i.e., sleep efficiency calculated from the record of sleep log is ≥85% or sleep onset latency of <1 hour) were excluded. The remaining patients were allocated to the active group and sham group at a ratio of 1:1, resulting in a total enrollment of 40 patients (20 in the active group and 20 in the sham group) (Figure 5).

Table 16. Outline of the exploratory study

Category	Details
Study objective	To compare the efficacy and safety in the active group (CBT-I with SUSMED App) with those in the sham app group (sham app has no CBT-I functions)
Type of study	Sham-controlled, multi-center, dynamic allocation, parallel-group double-blind study
Study population	Patients with insomnia
Inclusion criteria	Same as the pivotal clinical study
Exclusion criteria	Same as the pivotal clinical study
Sample size	40 patients
Method of use	Same as the pivotal clinical study
Testing/monitoring items and time frame	Same as the pivotal clinical study
Duration of use	57 days
Follow-up period	78 days
Concomitant drugs/treatments	Same as the pivotal clinical study
Study period	Same as the pivotal clinical study

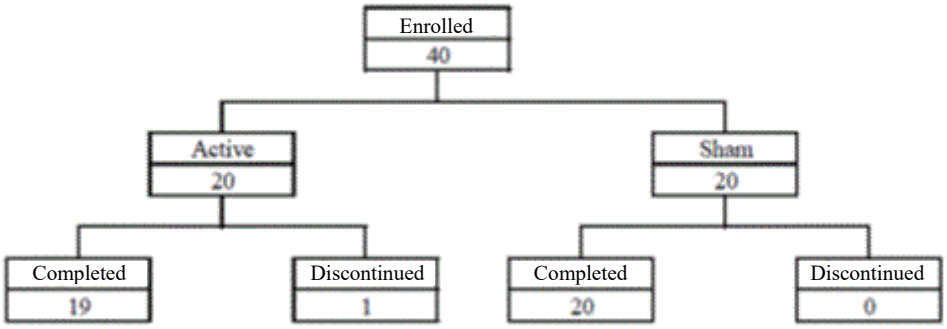


Figure 5. Disposition of patients

6.A.(2).1) Characteristics of patients

Table 17 shows the characteristics of patients enrolled in the study.

Table 17. Patient characteristics

		Active	Sham
N		20	20
Age	Mean	48.3	44.2
	20-29	0	1
	30-39	5	5
	40-49	6	7
	50-59	7	7
	60-69	2	0
Sex	Male	9	8
	Female	11	12
BMI (kg/m^2)	Mean	22.3	22.5
Prior medical history or comorbidity	Yes	7	6
	No	13	14
Baseline AIS	Mean	13.7	12.7

6.A.(2).2) Study results

6.A.(2).2).(a) Efficacy endpoints

The change in AIS from baseline to Week 8 (mean ± SD), the primary endpoint, was −7.4 ± 3.6 in the active group and −4.6 ± 5.2 in the sham group.

The change in AIS (item-by-item) from baseline to Week 8 (mean ± SD), the secondary endpoints, was as follows:

- Sleep induction (time required to fall asleep after going to bed): −1.3 ± 0.5 (active) and −1.1 ± 0.8 (sham)
- Awakenings during the night: −1.0 ± 0.7 (active) and −0.4 ± 0.9 (sham)
- Awakening earlier than desired and unable to fall back to sleep: −0.6 ± 0.8 (active) and −0.5 ± 0.8 (sham)
- Total sleep duration: −0.9 ± 0.7 (active) and −0.5 ± 0.9 (sham)
- Overall quality of sleep: −1.1 ± 0.6 (active) and −0.9 ± 0.7 (sham)
- Sense of well-being during the day: −1.0 ± 0.8 (active) and −0.6 ± 1.1 (sham)
- Physical and mental functioning capacity during the day: −0.8 ± 0.8 (active) and −0.5 ± 0.9 (sham)
- Sleepiness during the day: −0.8 ± 0.6 (active) and −0.4 ± 0.8 (sham)

The CGI-I from baseline to Week 8 was 1.6 ± 0.8 in the active group and 1.0 ± 0.9 in the sham group. The proportion of patients with an AIS of <6 points at Week 8 or treatment discontinuation was 52.6% in the active group and 35.0% in the sham group. As for the necessity of medications at the end of study or treatment discontinuation, no patients in either group required medications at the end of study.

6.A.(2).2).(b) Safety endpoints

A total of 7 adverse events were reported (Table 18): 5 events (in 4 patients) in the active group and 2 events (in 1 patient) in the sham group. More than 1 event was reported for nasopharyngitis in the active group and purulence in the sham group. There were no adverse events for which a causal relationship to the study device could not be ruled out.

Table 18. List of adverse events

Adverse event (PT)	Regardless of causal relationship				A causal relationship cannot be ruled out[1)]			
	Active		Sham		Active		Sham	
	n	Incidence (%)	n	Incidence (%)	n	Incidence (%)	n	Incidence (%)
Total	5	20	2	5	0	0	0	0
Purulence	0	0	2	5	0	0	0	0
Nasopharyngitis	2	5	0	0	0	0	0	0
Myalgia	1	5	0	0	0	0	0	0
Headache	1	5	0	0	0	0	0	0
Hordeolum	1	5	0	0	0	0	0	0

1) 1 = Definitely related; 2 = Probably related; 3 = Possibly related; 4 = Unlikely to be related

6.A.(3) Clinical study of the predecessor app (Study period, [redacted], 20[redacted] to [redacted], 20[redacted])

A sham-controlled, multi-center, dynamic allocation, parallel-group double-blind study was conducted in Japan to evaluate the efficacy and safety of the predecessor app in patients aged ≥20 years who were diagnosed with insomnia according to ICSD-3 and required treatment (Table 19). The change in AIS from baseline to Week 8 in the group receiving CBT-I with the predecessor app (predecessor app group) was compared with that in the group using a sleep hygiene education app (Table 20) (sleep hygiene group). Patients were allocated at a ratio of 1:1, resulting in a total enrollment of 118 patients (59 in the predecessor app group and 59 in the sleep hygiene group).

Table 19. Outline of the clinical study of the predecessor app

Category	Details
Study objective	To assess the efficacy of 8-week CBT-I using the predecessor app (predecessor app group) versus a sleep hygiene education-based software (sleep hygiene group) in patients with insomnia (as defined in ICSD-3) using AIS as the primary endpoint.
Type of study	Sham-controlled, multi-center, dynamic allocation, double-blind study
Study population	Patients with insomnia (according to ICSD-3)
Key inclusion criteria	Patients diagnosed with insomnia according to ICSD-3 who require treatment
Key exclusion criteria	(1) Patients with AIS of <9 points at enrollment (2) Patients whose sleep status during the period of ≥7 days before the enrollment date cannot be obtained from the sleep log
Sample size	110 patients
Evaluation method	Primary endpoint: change in AIS from baseline (before the start of study) to Week 8

Category	Details
Method of use	The study device (app) was downloaded on the patient's smart phone and the app program was used for 56 days.
Follow-up period	57 days
Main results	Patient characteristics: The mean age of patients was 44.4 years in the predecessor app group and 46.7 years in the sleep hygiene group. The most common age group was ≥40 years and <65 years (35 patients each in both groups). The predecessor app group had more men (31 patients) than women (24 patients) and the sleep hygiene group had more women (33 patients) than men (24 patients). The mean body mass index (BMI) was higher in the predecessor app group (22.5) than in the sleep hygiene group (21.9). At baseline, the mean AIS was 12.5 in the predecessor app group, and 12.8 in the sleep hygiene group, while the mean Quick Inventory of Depressive Symptomatology (QIDS) was 4.7 in the predecessor app group, and 4.4 in the sleep hygiene group. Study results: (1) Efficacy endpoints Baseline AIS scores, 12.5 in the predecessor app group and 12.8 in the sleep hygiene group, decreased to 5.3 in the predecessor app group and 5.4 in the sleep hygiene group at Week 8. The change from baseline was −7.2 in the predecessor app group and −7.4 in the sleep hygiene group, indicating that the change was not statistically significant. (2) Safety endpoints The incidence of adverse events was 66.1% in the predecessor app group and 64.4% in the sleep hygiene group. Both groups reported a high incidence of sleepiness (62.7% in both groups). Sleepiness was the only adverse event for which a causal relationship to the study device could not be ruled out in either group. Sleepiness occurred in 5 patients in the predecessor app group and 4 patients in the sleep hygiene group. The incidence of malfunctions was 8.5% in the predecessor app group and 11.9% in the sleep hygiene group. Karolinska Sleepiness Scale (KSS) was 3.8 in the predecessor app group and 4.0 in the sleep hygiene group at baseline and 4.8 in the predecessor app group and 3.9 in the sleep hygiene group at Week 8.
Number of study centers	[redacted]

Table 20. Similarity and difference between the sleep hygiene education app and predecessor app

Function	Sleep hygiene education app	Predecessor app
Terms of use	✓	✓
Entry of patients characteristics data	✓	✓
Entry of target bedtime and target rising time	✓	✓
AIS assessment	✓	✓
Contact	✓	✓
Tutorial	✓	✓
Push notification	✓	✓
Use discontinuation dialog	✓	✓
Sleep log	✓	✓
Sleep hygiene education	✓	✓
Stimulus control therapy	None	✓
Sleep restriction therapy	None	✓
Sleepiness test	✓	✓
Cognitive therapy	(Talking Control)[vi]	✓

6.B Outline of the review conducted by PMDA

PMDA's review focused on the following points, taking into account the comments from the Expert Discussion.

6.B.(1) Clinical significance of SUSMED App

The applicant's explanation about the clinical significance of SUSMED App:

The efficacy of CBT-I and how face-to-face CBT-I has been implemented in Japan were discussed earlier in Section "1.(1) History of development."

SUSMED App has been developed to perform CBT-I, a treatment approach to insomnia, in a routine medical practice using an app, and has functions equivalent to CBT-I (Table 2). The functions of SUSMED App including stimulus control therapy and sleep restriction therapy, core techniques of CBT-I mentioned earlier, were demonstrated to be effective; therefore, SUSMED App is considered to be a treatment option for patients with insomnia.

PMDA's view:

As described in Section "1.(1) History of development," more sleeping drugs are prescribed for patients with insomnia in Japan than in the US and Europe. The Japanese Clinical Guidelines state that sleeping drugs have problems as they cause adverse reactions and, in some patients, dependance associated with long-term use. CBT-I has been recommended as a first-line treatment for insomnia outside Japan. The Japanese Clinical Guidelines also recommend that

[vi] Instead of visualization of worries and thoughts as in cognitive therapy, this function displays 3 themes at random from hobbies, news, friends, holidays, self, and family, and allows the patient to engage in free writing on the theme selected by the patient.

psychological/behavioral interventions should be initiated as early as possible, with CBT-I cited as a representative intervention. As explained by the applicant, under circumstances in which CBT-I is not widely practiced in Japan, SUSMED App has been developed to perform CBT-I using software. To ensure its proper use, SUSMED App should be used by physicians with thorough knowledge of CBT-I. If insomnia symptoms are improved by using SUSMED App in accordance with the proper use guidelines, which are discussed later in Section "6.B.(6) Clinical positioning," it is clinically meaningful to introduce SUSMED App as a treatment option for patients with insomnia symptoms.

6.B.(2) Appropriateness of the design of the pivotal clinical study

PMDA's view:

Since the pivotal clinical study used a subjective endpoint as the primary endpoint, the design of the pivotal clinical study, namely comparison with the sham app, was appropriate. The sham app, is required to have no functions associated with the efficacy of SUSMED App, and the blindness should be ensured. Therefore, PMDA asked the applicant to explain whether the appropriateness of the sham app and blindness were maintained.

The applicant's explanation:

Table 6 shows the main functions of the sham app, which are (a) setting of the target bedtime and target rising time, which were determined after discussion between the primary care physician and the patient) and (b) recording of the assessment of AIS, etc. once a week. The sham app functions do not have any element of CBT-I.

To maintain blindness, [redacted] Furthermore, the staff at the study centers did not inform patients about the content of SUSMED App or the sham app and did not access data on patients' mobile devices from the time of consent, initial setting, the start of app use, through to the end of app use. Explanation of the use of SUSMED App or the sham app to patients or inquiries [redacted] The system audit and study center audit inspected the procedures and structures for maintaining the blindness of the sponsor and study centers, and revealed no particular findings. In addition, patients who are aware that they are assigned to the sham group may request withdrawal from the study or become less likely to use the sham app, and the intervention effect of the sham app may disappear in such patients. In either group of the pivotal clinical study, however, no patients discontinued the study during for the reason of being assigned to the sham app or for any other reasons. Moreover, adherence to medical device use

was 89.3% in the active group and 100% in the sham group, indicating no decrease in the use of sham app. Based on the above, the applicant considers that blindness was maintained.

PMDA's view:
The functions of the sham app used in the pivotal clinical study do not have any element of CBT-I that has therapeutic effects on insomnia; therefore, there were no significant problems with the sham app. According to the applicant, blindness was maintained because 100% of patients continued to use the sham app; however, the applicant did not evaluate whether the patients recognized which app, SUSMED App or sham app, they were using. It is therefore difficult to determine whether blindness was maintained. Ideally, the efficacy of SUSMED App be should have been evaluated after confirming whether users recognized which of the apps they were using and determining how blindness was actually maintained in the pivotal clinical study. Nevertheless, it is acceptable to evaluate the efficacy of SUSMED App using the sham app as a control for the following reasons: (a) No patients discontinued treatment during the study period; (b) adherence to sham app use was 100%; and the applicant tried to ensure blindness by taking actions in the management of the study, as explained by the applicant, [see Section "6.B.(3) Efficacy" for details of efficacy evaluation of SUSMED App].

6.B.(3) Efficacy

6.B.(3).(a) Appropriateness of using subjective endpoints

The applicant's rationale for using subjective endpoints as the primary endpoint:
The Athens Insomnia Scale, developed under the initiative of the World Health Organization (WHO), is a tool to comprehensively evaluate the severity of insomnia symptoms: sleep onset latency, nocturnal awakening, early morning awakening, total sleep duration, sleep quality, restorative sleep, physical and mental functioning capacity during the day, and sleepiness during the day. The reliability and validity of the Japanese version of AIS have also been confirmed.

Subjective methods of evaluating insomnia include sleep diaries, questionnaires, and visual analog scale, while objective methods include polysomnography and actigraphy. The "Guidelines on the Clinical Evaluation of Sleeping Drugs"[17] provide the following precautions regarding the evaluation methods:

> "The objective evaluation methods are performed under an artificial sleep environment, which may be different from the everyday life conditions. In subjective evaluation methods, sleep stages or sleep structure cannot be evaluated. The results of an objective evaluation method do not necessarily correlate with those of a subjective method. It is important to evaluate the effect of a study drug on sleep structure, not only from the standpoint of efficacy but also in terms of safety. While clinical pharmacology and exploratory studies require evaluation with an

objective evaluation method, it is important to evaluate the self-perceived improvement effect under daily life conditions in an appropriate manner. Therefore, for the primary endpoint of a confirmatory study, assessment variables based on a subjective evaluation method should be established."

Unlike medications, CBT-I is known to improve insomnia symptoms by focusing on perpetuating factors, alleviating somatized tension and learned sleep-preventing associations. Unlike the evaluation of sleeping drugs, evaluation of SUSMED App, which is based on CBT-I, does not involve pharmacological evaluation and therefore does not require objective evaluation such as by polysomnography.

Based on the above, the primary endpoint for the efficacy evaluation of SUSMED App should include not only insomnia symptoms (e.g., difficulty initiating sleep, nocturnal awakening, early morning awakening) but also sleep quality and a subjective endpoint that can evaluate "daytime functioning capacity on the next day," a true outcome. Accordingly, AIS was selected as the primary endpoint. To evaluate individual insomnia symptoms more objectively, the following were selected as secondary endpoints: change in AIS, item-by-item, from baseline; sleep onset latency based on sleep diary and actigraph data; nocturnal awakening; change in sleep efficiency from baseline, general assessment by the physician (CGI-I), and the proportion of patients with an AIS of <6 points.

PMDA's view:
Some patients with insomnia are known to present with insomnia symptoms and impaired physical/mental functioning the next day, and the purpose of insomnia treatment is to improve daytime functioning capacity through a good sleep.[7] The "Guidelines on the Clinical Evaluation of Sleeping Drugs" state that "sleep onset latency, duration and number of nocturnal awakenings, total sleep duration, sleep quality, restorative sleep, and physical/mental functioning the next day" should be evaluated in order to assess the efficacy profile of a drug for insomnia symptoms and for impaired physical/mental functioning on the next day. Based on the above, the primary efficacy endpoint selected by the applicant for evaluating insomnia treatment is reasonable because the endpoint can comprehensively assess "sleep onset latency, nocturnal awakening, early morning awakening, total sleep duration, sleep quality, restorative sleep, daytime physical/mental functioning capacity, and daytime sleepiness," which include evaluation of daytime functioning capacity on the next day, the purpose of insomnia treatment. However, sleep structure or sleep stages have not been evaluated, and no results of physiological evaluation on sleep improvement have been obtained. The applicant should inform healthcare professionals, etc. that evaluation by polysomnography has not been conducted via the instructions for use and other materials.

6.B.(3).(b) Efficacy

To interpret the results of the efficacy of SUSMED App obtained from the pivotal clinical study, PMDA considered that the following should be evaluated and asked the applicant to explain the following:

- Reasons the results of the change in AIS from baseline to Week 8 are clinically useful
- Reasons SUSMED App showed no superiority over the sham app in nocturnal awakening-related endpoints
- Reasons the results of the secondary endpoints are clinically useful

The applicant's explanation:

- Reasons the results of the change in AIS from baseline to Week 8 are clinically useful

In clinical research[18] in which face-to-face CBT-I sessions were provided to 26 patients with insomnia for 8 to 10 weeks using AIS as an endpoint, the change in AIS from baseline to the end of treatment was 6.5. Based on the results, the level of efficacy of SUSMED App is considered to be equivalent to the efficacy of face-to-face CBT-I as shown by the pivotal clinical study, and therefore, there should be no problem with the use of the app in clinical practice.

- Reasons SUSMED App showed no superiority over the sham app in nocturnal awakening-related endpoints

The mean number of nocturnal awakenings based on the sleep log at baseline was 1.3 times in the active group and 1.4 times in the sham group. This suggests that the pivotal clinical study may have not enrolled patients with problematic nocturnal awakenings, which may have led to no difference in the endpoints.

- Reasons the results of secondary endpoints are clinically useful

SUSMED App is useful in clinical practice because the results of secondary endpoints were as follows:

- The proportion of patients with improved CGI-I (general assessment by the physician) (5 = minimally improved, 6 = much improved, or 7 = very much improved) was 83.9% (73 of 87 patients) in the active group and 50.0% (44 of 88 patients) in the sham group.
- The proportion of patients with an AIS of <6 points, a cut-off value below which insomnia treatment is not required, was 37.9% (33 of 87 patients) in the active group and 10.2% (9 of 88 patients) in the sham group.
- The proportion of patients who did not require medications at the end of the pivotal clinical study 93.0% (80 of 87 patients) in the active group and 85.2% (75 of 88 patients) in the sham group.

In addition, clinical research (reference data) was conducted by recruiting patients using the same inclusion and exclusion criteria as those of the pivotal clinical study, and Zolpidem Tartrate Tablet 5 mg (Myslee® Tablets or its generic drugs) was administered once daily before getting into bed for 8 weeks to evaluate the change in AIS. Table 21 shows the results of change in AIS in the clinical research and in the pivotal clinical study. The proportion of patients who were diagnosed as requiring medications by the physician at the end of the study was as low as 7.0% in the active group of the pivotal clinical study, compared with 26.3% in the research of Myslee. This suggests that SUSMED App is clinically useful.

Table 21. Change in AIS in the pivotal clinical study and clinical research of Myslee

Study	Group	Baseline	Week 8	Week 10	Proportion of patients requiring medications (Week 8) (%)
		Mean	Mean	Mean	
Pivotal clinical study	Sham	13.6	10.4	9.7	14.8
	Active	13.4	6.7	5.9	7.0
Myslee clinical research	Sleeping drug	13.4	3.5	5.5	26.3

PMDA's view on the efficacy results and their interpretation:

The development concept for SUSMED App is to offer CBT-I similar to that offered in face-to-face sessions through application software. The applicant's idea of explaining the clinical usefulness of SUSMED App by comparing its level of effects with that of face-to-face CBT-I is understandable. However, the patient characteristics, study conditions, and other factors in literature reports differ from those of the pivotal clinical study, precluding a straightforward comparison. In addition, only a few literature reports on this topic can be used as references. PMDA therefore cannot concluded that SUSMED App has a similar level of efficacy as face-to-face CBT-I. Moreover, the effect size in the sham group should be taken into account when assessing the effect size in the active group. PMDA therefore cannot accept the applicant's explanation.

The results of the primary endpoint show that AIS improved to 6.7 at Week 8 and 5.9 at Week 10 by using SUSMED App. The superiority of SUSMED App to the sham app was also demonstrated. As for the secondary endpoints, as explained by the applicant, the pivotal clinical study did not appropriately evaluate nocturnal awakening-related endpoints ("awakenings during the night" in Table 10, "number of nocturnal awakenings" in Tables 14 and 15), and therefore failed to demonstrated the superiority of SUSMED App to the sham in these endpoints. SUSMED App was shown to be superior to the sham app in the other secondary endpoints. The pivotal clinical study also evaluated (a) the proportion of patients with an AIS of <6 points, a cut-off value below which insomnia treatment is not required (Table 12) and (b) the proportion of patients who were

diagnosed by the physician as not requiring medication at the end of the study (Table 13); the results suggest that SUSMED App is clinically useful.

Based on the results of the review discussed later in Section "6.B.(5) Comprehensive risk-benefit balance evaluation," PMDA considers that the efficacy of SUSMED App is acceptable provided that the following actions are taken by the applicant:

- As explained by the applicant, the superiority of SUSMED App over the sham app in the nocturnal awakening-related endpoints was not appropriately evaluated. Therefore, using the instructions for use and other materials, the applicant should appropriately inform healthcare professionals, etc. that these nocturnal awakening-related endpoints have not been evaluated. PMDA instructed the applicant to take this action and the applicant followed the instruction.
- Since CBT-I is expected to have long-lasting effects, the applicant should appropriately inform healthcare professionals, etc. that the long-term efficacy has not been evaluated via the instructions for use and other materials, and should evaluate the long-term efficacy through the use-results survey, etc. PMDA instructed the applicant to take these actions and the applicant followed the instruction.

6.B.(4) Safety

PMDA asked the applicant to explain the following safety issues associated with SUSMED App:

- The pivotal clinical study reported no adverse events for which a causal relationship to SUSMED App could not be ruled out or malfunctions leading to serious adverse events, but the study enrolled only a small number of patients. Explain the expected risks associated with the use of SUSMED App in clinical practice in Japan.
- The clinical study of the predecessor app reported a higher incidence of sleepiness (62.7% both in the predecessor app group and sleep hygiene group) than the pivotal clinical study. Explain the reason.

The applicant's response:

- Expected risks associated with the use of SUSMED App in clinical practice in Japan

The number (frequency) of clinic visits may decrease in patients using SUSMED App in clinical practice compared with the clinical study patients. Face-to-face CBT-I sessions are delivered with a total of 4 to 6 sessions, each lasting approximately 50 minutes. CBT-I with a total of 4 sessions every other week has been reported to be generally highly effective, which translates to 1 session every 2 weeks.

Patients using SUSMED App in clinical practice receive CBT-I sessions via the app. Therefore they may not have to visit the clinic for sessions, resulting in decreased number of clinic visits

compared with patients receiving face-to-face CBT-I sessions. For this reason, an increase in risk as a result of decreased number of clinic visits (frequency) was examined. Since face-to-face CBT-I has a lower risk in terms of safety, and no special precautions have been provided regarding clinic visits for safety evaluation, it is therefore considered unlikely that a reduction in clinic visits (frequency) will increase risk.

- Sleepiness was reported at a higher incidence in the clinical study of the predecessor app than in the pivotal clinical study

In the clinical study of the predecessor app, the adverse event of sleepiness was defined as "worsening of KSS from the previous day (change from ≤6 points to ≥7 points)." In contrast, in the pivotal clinical study, "daytime sleepiness reported by patients" was defined as an adverse event; this allowed the pivotal clinical study to more appropriately evaluate "daytime sleepiness," an adverse reaction to SUSMED App.

PMDA's view on the safety of SUSMED App:
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; therefore, PMDA concludes that the clinical study data indicate no significant problems in terms of the safety of SUSMED App. The applicant also explained that the number of clinic visits (frequency) may decrease in patients in clinical practice compared with the clinical study patients; however, the probability of a decrease in the number of clinical visits differs depending on the patient's symptoms; therefore, it is not necessary to define the number of clinic visits (frequency) in the instruction for the use of SUSMED App. Meanwhile, the cognitive therapy incorporated in SUSMED App only visualizes worries and thoughts, and does not provide cognitive intervention to correct insomnia-associated thinking; this lack of appropriate action to address the wrong worry or thought patterns may worsen insomnia symptoms. The applicant should ensure that physicians well-versed in face-to-face CBT-I select eligible patients and properly use SUSMED App, as risk minimization activities, and the proper use guidelines to be prepared by the relevant academic societies should be followed.

In addition, face-to-face CBT-I and sleep restriction therapy incorporated in CBT-I have been reported to increase subjective sleepiness, malaise, difficulty concentrating, cumulative fatigue, poor concentration, and other symptoms. This information and data on the adverse event of sleepiness from the study of the predecessor app should be included in the instructions for use and other materials. PMDA instructed the applicant to take action accordingly.

Based on the above, PMDA concluded that there was no particular problem with the safety of SUSMED App, provided that the app is used properly by following the proper use guidelines prepared by the relevant academic societies.

To ensure the safety of SUSMED App in clinical practice, the applicant should continue to evaluate safety data from the use-results survey, etc., and take actions such as ensuring proper use, as necessary.

6.B.(5) Comprehensive risk-benefit balance evaluation

PMDA's view on the risk-benefit balance based on the review on the efficacy and safety of SUSMED App:

Although whether blindness was maintained in the sham group has not been confirmed, the results of the primary endpoint demonstrated the superiority of SUSMED App over the sham app in efficacy, and the results of secondary endpoints suggested that SUSMED App had clinical usefulness.

Patients receiving face-to-face CBT-I may experience adverse events of subjective sleepiness, malaise, difficulty concentrating, cumulative fatigue, and poor concentration. These events may also occur in patients using SUSMED App, but such risk is less significant compared with the adverse reactions to pharmaceuticals.

After evaluating the risk-benefit balance based on the efficacy and safety results from the pivotal and other clinical studies, PMDA considers that SUSMED App is clinically useful in the population eligible for the pivotal clinical study because currently many patients who should, or wish to, receive CBT-I do not have access to CBT-I due to the lack of its availability in clinical practice.

6.B.(6) Clinical positioning

PMDA asked the applicant to explain the rationale for including patients with secondary insomnia in the target population for SUSMED App despite that they were excluded from the pivotal clinical study:

The applicant's explanation:

Because treatment with SUSMED App requires patients to understand sleep correctly and to keep a sleep diary, patients with secondary insomnia associated with psychiatric disorder, etc. may not be able to continue receiving treatment with SUSMED App when priority is given to treatment of the primary illness. Therefore, the risk of drop-out from treatment can be minimized by examining

in advance whether the patient can clearly understand information provided by SUSMED App and continue to use the app, based on the status of the patient's primary illness.

PMDA's view on eligible patients:
Patients are diagnosed with insomnia without distinction between primary and secondary insomnia. As a result, patients considered to have primary insomnia at the initial visit may be diagnosed later as having secondary insomnia. It is considered difficult to distinguish primary insomnia from secondary insomnia. There is no distinction in treatment between primary and secondary insomnia, and the same treatments are offered. As explained by the applicant, there are patients with secondary insomnia who are not suitable for treatment with SUSMED App because of the influence of the primary illness. Therefore, whether patients are ineligible for treatment with SUSMED App should be determined by physicians well-versed in CBT-I who are fully aware of the limitations of SUSMED App. PMDA considers that including patients with secondary insomnia in the target population is acceptable, provided that the proper use guidelines (including the rationale for the indication) are followed, and that the instructions for use and other materials state that patients with secondary insomnia were excluded from the pivotal clinical study and the exploratory study.

The applicant also explained that if SUSMED App is clinically positioned as CBT-I as recommended in the treatment algorithm (Figure 2) of the Japanese Clinical Guidelines, SUSMED App can be used for the following reasons:
Components of CBT-I, including the sleep scheduling technique, are incorporated into SUSMED App. The sleep scheduling technique, a combination of stimulus control therapy and sleep restriction therapy, is regarded as the core technique of CBT-I. The results from the pivotal clinical study demonstrated that SUSMED App had an efficacy equivalent to that of face-to-face CBT-I, and its efficacy level is as expected for an app providing cognitive behavioral therapy to treating insomnia. SUSMED App is expected to be used as a first-line treatment from an early stage of treatment, which will not preclude its use in combination with pharmacotherapy, or as a second-line treatment.

PMDA's view on the clinical positioning of SUSMED App:
The manual of cognitive behavioral therapy for insomnia recommends that specific CBT-I treatment tailored to individual patients should be provided. According to several reports,[19,20,21] the CBT-I programs that are offered according to the skill level of healthcare staff, severity and comorbidity of patients include stepped care models, ranging from self-help treatment with information provision, simplified less intensive treatment, group therapy, and intensive individual therapy, and that these programs should be developed according to the situation of healthcare

services in each country. Although some components (functions) of CBT-I are incorporated in SUSMED App have (Table 2), the app is not intended to provide treatment individually tailored to the patient's condition. In addition, whether SUSMED App is as effective as face-to-face CBT-I has not been evaluated. At the Expert Discussions, the expert advisors stated that communication with insomnia patients is important in psychotherapy and, if treatment does not work, their symptoms may worsen. Based on the above, SUSMED App should be positioned as a treatment option available for physicians who provide insomnia treatment including face-to-face CBT-I, and it is important to determine whether SUSMED App is suitable for individual patients before use.

Based on the above review, the target patients of SUSMED App should be those who are eligible for face-to-face CBT-I according to the manual of cognitive behavioral therapy for insomnia, prepared by the Japanese Society of Sleep Research. The pivotal clinical study demonstrated the efficacy and safety of SUSMED App and suggested the effectiveness and safety of the app in the target patients in Japan. The risk-benefit balance of SUSMED App in patients with insomnia can be ensured by undertaking the post-marketing safety activities presented in Sections "6.B.(3) Efficacy," "6.B.(4) Safety," and "6.B.(7) Post-marketing safety activities including proper use." Based on the clinical positioning of SUSMED App, the intended use or indication should be modified as shown below (Underline denotes additions).

Intended use or indication

<u>To perform cognitive behavioral therapy for</u> the treatment of insomnia.

6.B.(7) Post-marketing safety activities including proper use

PMDA's view:

No medical devices offering CBT-I using a digital app have been introduced in clinical practice. In order to introduce SUSMED App, a highly novel product in Japan, as a more effective and safer medical device, the app should be used by physicians well-versed in face-to-face CBT-I who are familiar with the characteristics of SUSMED App, and eligible patients should be selected in an appropriate manner. Therefore, the proper use guidelines for SUSMED App should be prepared by the relevant academic societies. Based on the results of the use-results survey, the proper use guidelines should be revised and additional safety activities should be undertaken as necessary.

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

7.A Summary of the data submitted

The applicant considered that SUSMED App need not be designated as a medical device subject to a use-results evaluation, and therefore did not submit the plan for post-marketing surveillance, etc.

7.B Outline of the review conducted by PMDA

PMDA's view:

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; this lack of appropriate action to address the wrong worry or thought patterns may worsen insomnia symptoms. Therefore, the applicant should continue to evaluate the safety of SUSMED App in clinical practice through a use-results survey or by other means, and should take actions such as ensuring proper use, as necessary. In addition, the applicant should gather the following information on the efficacy of SUSMED App in clinical practice: long-term efficacy, which was not evaluated in the pivotal clinical study; nocturnal awakenings; and the effects of minor changes such as modification of wording on the efficacy. PMDA asked the applicant to submit the plan for post-marketing surveillance, etc.

The applicant submitted the outline of use-results survey (Table 22).

Table 22. Outline of use-results survey (draft)

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 marketing approval date (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])

The rationale for the sample size:

The results of the pivotal clinical study suggest that serious adverse events for which a causal relationship to SUSMED App could not be ruled out are unlikely to occur. Therefore, the main

objective of this use-results survey is to examine the safety profile of SUSMED App in clinical practice, and this can be achieved by evaluating adverse events occurring at relatively high frequency. The planned sample size is at least 300 patients because this sample size can detect an adverse event with an incidence of 1% with a power of 95%. While the pivotal clinical study (N = 175) was conducted at 9 study centers, 20 survey sites were selected in order to evaluate the use results at multiple medical institutions including those not specializing in sleep disorders.

PMDA accepted the outline of use-results survey for SUSMED App.

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

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

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

IV. Overall Evaluation

The SUSMED App is application software installed on mobile devices and used for receiving CBT-I. The pivotal clinical study evaluated the efficacy of SUSMED App for improving insomnia symptoms and its safety in patients aged ≥20 years who were diagnosed with insomnia according to ICSD-3 and required treatment. The review of the product focused on (1) the risk-benefit balance based on the efficacy and safety of SUSMED App; (2) clinical positioning; and (3) post-marketing safety activities including the proper use of SUSMED App. Taking account of comments raised at the Expert Discussion, PMDA reached the following conclusions:

(1) Risk-benefit balance based on the efficacy and safety of SUSMED App

Although whether blindness in the sham group was maintained has not been confirmed, the results of the primary efficacy endpoint show that AIS improved to 6.7 at Week 8 and 5.9 at Week 10. The superiority of SUSMED App over the sham app was also demonstrated. As for the secondary endpoints, the pivotal clinical study did not appropriately evaluate nocturnal awakening-related endpoints ("awakenings during the night" in Table 10, "number of nocturnal awakenings" in Tables 14 and 15), and therefore failed to demonstrated the superiority of SUSMED App to the sham in these endpoints. SUSMED App was shown to be superior to the sham app in the other secondary endpoints. The pivotal clinical study also evaluated (a) the proportion of patients with

an AIS of <6 points, a cut-off value below which insomnia treatment is not required and (b) the proportion of patients who were diagnosed by the physician as not requiring medication at the end of study; the results suggest that SUSMED App is clinically useful.

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 or malfunctions leading to serious adverse events; therefore, PMDA has concluded that the clinical study results indicate no significant problems in terms of the safety of SUSMED App. Meanwhile, the cognitive therapy incorporated in SUSMED App only visualizes worries and thoughts, without providing cognitive intervention to correct insomnia-associated thinking; this lack of appropriate action to address the wrong worry or thought patterns may worsen insomnia symptoms. However, these risks are less significant compared with the adverse reactions to pharmaceuticals. After evaluating the risk-benefit balance based on the efficacy and safety results from the pivotal and other clinical studies, PMDA has concluded that SUSMED App is clinically useful, because making the app available in clinical practice is meaningful in the current situation where many patients who should, or wish to, receive CBT-I do not have access to CBT-I due to the lack of its availability in clinical practice.

Physicians well-versed in face-to-face CBT-I should select eligible patients and properly use SUSMED App, which constitute risk minimization activities. Therefore SUSMED App should be used according to its proper use guidelines to be prepared by the relevant academic societies. In addition, face-to-face CBT-I and sleep restriction therapy incorporated in CBT-I have been reported to increase subjective sleepiness, malaise, difficulty concentrating, cumulative fatigue, poor concentration, and other symptoms. This information and data on the adverse event of sleepiness from the study of the predecessor app should be included in the instructions for use and other materials.

(2) Clinical positioning

The manual of cognitive behavioral therapy for insomnia recommends that specific CBT-I treatment tailored to individual patients should be provided. According to several reports, the CBT-I programs that are offered according to the skill level of healthcare staff, severity and comorbidity of patients include stepped care models, ranging from self-help treatment with information provision, simplified less intensive treatment, group therapy, and intensive individual therapy, and these programs should be developed according to the situation of healthcare services in each country. Although some components (functions) of CBT-I are incorporated in SUSMED App, the app is not intended to provide individually tailored treatment based on the patient's condition. In addition, whether SUSMED App is as effective as face-to-face CBT-I has not been evaluated. At the Expert Discussions, the expert advisors stated that communication with

insomnia patients is important in psychotherapy and, if treatment does not work, their symptoms may worsen. Based on the above, SUSMED App should be positioned as a treatment option available for physicians who provide insomnia treatment including face-to-face CBT-I, and it is important to determine whether SUSMED App is suitable for individual patients before use.

Based on the above review, the target patients of SUSMED App should be those who are eligible for face-to-face CBT-I according to the manual of cognitive behavioral therapy for insomnia, prepared by the Japanese Society of Sleep Research. Based on the clinical positioning of SUSMED App, the intended use or indication should be modified as shown below (Underline denotes additions).

Intended use or indication

To perform cognitive behavioral therapy for the treatment of insomnia.

(3) Post-marketing safety activities including the proper use of SUSMED App

No medical devices providing CBT-I using a digital app have been introduced in clinical practice. In order to introduce the highly novel device SUSMED Appin Japan as a more effective and safer medical device, it is important to ensure that the app is used by physicians well-versed in face-to-face CBT-I who are familiar with the characteristics of SUSMED App, and that patients' eligibility is determined appropriately. Therefore, the proper use guidelines for SUSMED App should be prepared by the relevant academic societies. Based on the results of the use-results survey, the proper use guidelines should be revised and additional safety activities should be undertaken as necessary. The period of survey for the use-results evaluation (use-results survey) should be 3 years and 11 months (preparation period, 1 year; enrollment period, 2 years; follow-up period, 8 months at the maximum [observation, 2 months; follow-up, 6 months maximum for each patient]; analysis period, 3 months).

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

Intended Use

To perform cognitive behavioral therapy for the treatment of insomnia.

Approval Conditions

The applicant is required to take necessary actions, such as disseminating the proper-use guidelines prepared in cooperation with the relevant academic societies and providing training programs, to ensure that the product is used only by physicians with sufficient knowledge of

insomnia who have acquired thorough knowledge of cognitive behavioral therapy for insomnia (CBT-I) and the CBT-I program provided by the product.

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 evaluation. The period of survey for the use-results evaluation (use-results survey) should be 3 years and 11 months.

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

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