June 19, 2020
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 21 Organ function testing apparatus
Term Name	Smoking Cessation Treatment Support System
Brand Name	CureApp SC Digital Therapeutic and CO Checker for Nicotine Dependence
Applicant	CureApp, Inc.
Date of Application	December 6, 2019 (Application for marketing approval)

Results of Deliberation

In its meeting held on June 19, 2020, 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 without designation as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

Review Report

May 28, 2020

Pharmaceuticals and Medical Devices Agency

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

Classification	Instrument & Apparatus 21 Organ function testing apparatus
Term Name	Smoking Cessation Treatment Support System (to be newly created)
Brand Name	CureApp SC Digital Therapeutic and CO Checker for Nicotine Dependence
Applicant	CureApp, Inc.
Date of Application	December 6, 2019
Reviewing Office	Office of Medical Devices I

Review Results

May 28, 2020

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Brand Name	CureApp SC Digital Therapeutic and CO Checker for Nicotine Dependence
Applicant	CureApp, Inc.
Date of Application	December 6, 2019

Results of Review

The "CureApp SC Digital Therapeutic and CO Checker for Nicotine Dependence" (hereinafter referred to as "the CASC system") is a smoking cessation treatment support system for patients with nicotine dependence used adjunct to the standard smoking cessation treatment program, which is specified in the Standard Procedure Manual for Smoking Cessation 7th edition [in Japanese] (co-edited by the Japanese Circulation Society, the Japan Lung Cancer Society, the Japanese Cancer Association, and the Japanese Respiratory Society). The CASC system consists of an exhaled carbon monoxide (CO) meter (CO checker), an application for patients (patient app), and the other application for physicians (doctor app).

When the patient measures exhaled CO level using the CO checker, the result is displayed on the app screen of both the patient's device and doctor's device. The patient app is installed on their own smartphone or other mobile device before use. According to the measured exhaled CO levels, smoking status, answers to the questions from the app, etc. entered by the patient, the patient app provides messages, educational videos, etc. to help the patient understand nicotine dependence and adjust themselves to their behavior change associated with smoking cessation. The doctor app is installed on the physician's workstation, etc. before use, and it provides patient data including the use status of the patient app, measured exhaled CO levels, etc.

The applicant submitted non-clinical data on the CASC system, i.e., electrical safety and electromagnetic compatibility, biological safety, mechanical safety, stability, durability, and performance, as well as evaluation data on the maintenance of accuracy in exhaled CO measurement under mechanical stress. The data revealed no particular problems.

Data relating to the clinical study of the CASC system submitted were the results of a randomized, open-label, parallel group study conducted in 584 subjects at 31 study centers in Japan. To evaluate efficacy, the continuous abstinence rate (CAR) from Weeks 9 to 24 in the CASC group was compared to that in the control group (the subjects used an application with [redacted] without functions that may contribute to efficacy). The CAR was 63.9% in the CASC group and 50.5% in the control group. In a logistic regression analysis using the type of smoking cessation drug as a covariate, the odds ratio for CAR in the CASC group to the control group and the 95% confidence interval (CI) at Week 24 was 1.73 [1.239-2.424], indicating a significant difference between groups ($P = 0.001$).

For safety evaluation, adverse events that occurred in the study were assessed. There were no adverse events for which a causal relationship to the CASC system or the control device could not be ruled out, suggesting that the system has acceptable clinical safety.

Based on comments from the Expert Discussion, PMDA comprehensively reviewed the data submitted, and concluded that there were no particular problems in the efficacy or safety of the CASC system.

On the basis of its regulatory review, PMDA has concluded that the CASC system may be granted marketing approval for the following intended use, and that this result should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

Intended Use
Assistance in smoking cessation treatment of patients with nicotine dependence

Review Report

May 28, 2020

Product for Review	
Classification	Instrument & Apparatus 21 Organ function testing apparatus
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Table of Contents

List of Abbreviations

BI	Brinkman index
CO	Carbon monoxide
FAS	Full analysis set
FTCQ-12	12-item French version of the Tobacco Craving Questionnaire
FTND	Fagerström test for nicotine dependence
ISO	International Organization for Standardization
JIS	Japanese Industrial Standard
KTSND	Kano Test for Social Nicotine Dependence
MPSS	Mood and Physical Symptoms Scale
TDS	Tobacco Dependence Screener

I. Product Overview

The “CureApp SC Digital Therapeutic and CO Checker for Nicotine Dependence” (hereinafter referred to as the “CASC system”) is a smoking cessation treatment support system for patients with nicotine dependence used adjunct to the standard smoking cessation treatment program, which is specified in the Standard Procedure Manual for Smoking Cessation 7th edition [in Japanese] (co-edited by the Japanese Circulation Society, the Japan Lung Cancer Society, the Japanese Cancer Association, and the Japanese Respiratory Society) (hereinafter referred to as “Standard Procedure”). The CASC system consists of an exhaled carbon monoxide (CO) meter[i] (CO checker), an application for patients (patient app), and the other application for physicians (doctor app).

When the patient measures exhaled CO level using the CO checker (Figure 1), the result is displayed on both the patient app and doctor app. The patient app is installed on their own smartphone or other mobile device before use. According to the measured exhaled CO levels, smoking status, answers to the questions from the app, etc. entered by the patient, the patient app provides messages, educational videos, etc. to help the patient understand nicotine dependence and adjust themselves to their behavior change associated with smoking cessation (

Figure 2 and Table 1). The doctor app is installed on the physician’s workstation, etc. before use, and it provides patient data including the use status of the patient app, measured exhaled CO levels (Figure 3 and Table 1).

The CASC system is used for a total of 24 weeks, i.e., 12 weeks of the standard smoking cessation treatment program and 12 weeks after the completion of the treatment program. The CASC system is available only on a physician’s prescription.

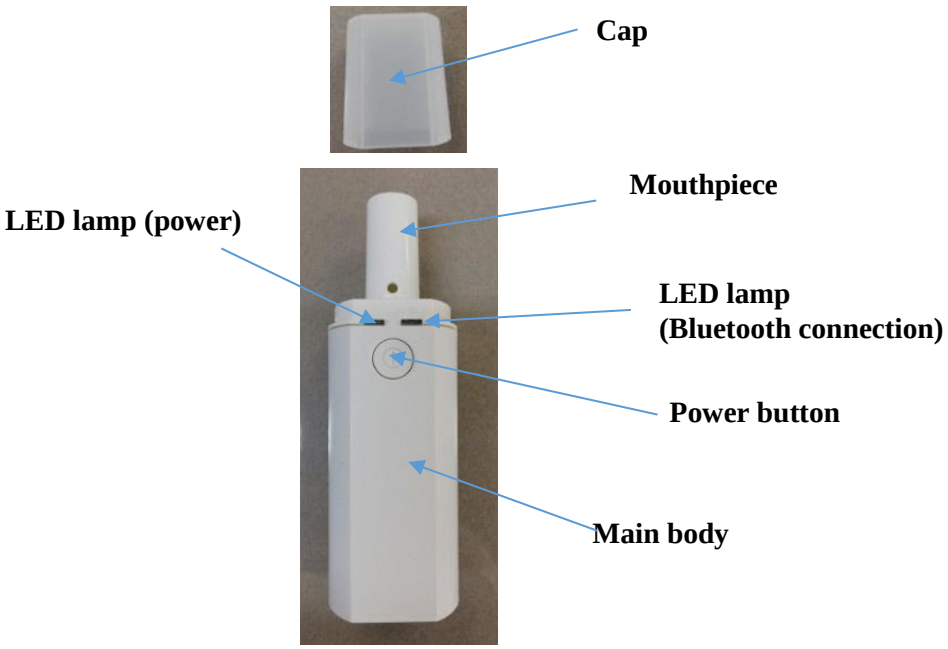
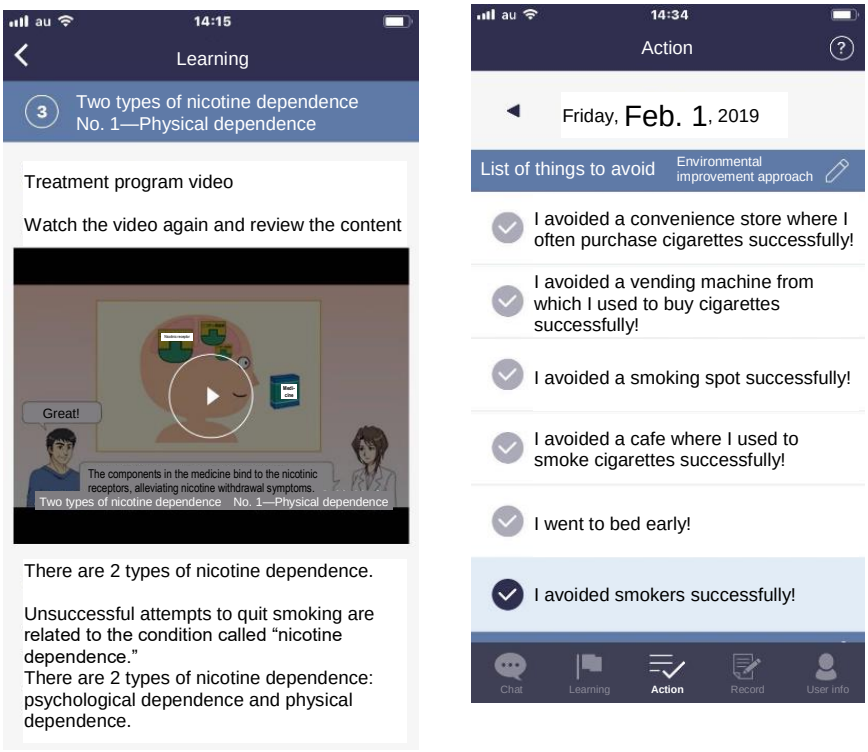


Figure 1. Appearance of CO checker

[i] Used for diagnosis as an objective indicator of smoking status.



*The patient app is available only in Japanese. This English translation is for information purposes only.

Figure 2. A sample display of the patient app

Figure 3. A sample display of the doctor app

Table 1. Main functions of the patient and doctor apps

	Function	Summary
Patient app	Treatment program	Delivers a message- and video-based treatment program that helps understand nicotine dependence and provides educational training on behavioral therapies (e.g., compensatory behavior, environmental improvement, behavioral pattern change, operant reinforcement, and self-assertiveness training).
	Action management	Displays a list of daily actions, allowing the patient to choose actions to take and keep a record of actions taken in behavioral therapy.
	Smoking cessation diary	Displays self-entered patient record such as physical condition, smoking cessation status, medication status, and actions taken.
	Chat	Delivers messages based on the self-entered information to encourage the patient to work on the smoking cessation treatment program, action function, and smoking cessation diary.
Doctor app	Patient data display	Displays patient information such as smoking cessation status, measured exhaled CO levels, and use status of the patient app.
	Diagnosis/treatment assistance	Displays guidance, etc. for smoking cessation treatment to assist physicians.

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

The data submitted by the applicant with the application and the applicant's response to inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors at the Expert Discussion on the CASC system declared that it does not fall under Item 5 of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

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

1.(1) History of development

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

Nicotine dependence is a type of drug dependence characterized by difficulty in quitting smoking by willpower alone. Nicotine dependence involves 2 types of dependence, namely, physical dependence and psychological dependence.[1] Physical dependence is associated with withdrawal symptoms, i.e., unpleasant symptoms such as anxiety and frustration without nicotine. Smoking cessation drugs are effective for physical dependence. A person with psychological dependence, in contrast, repeats smoking by custom or habit. Psychological dependence is a condition with increased urge to smoke, which is triggered in situations linked to their habitual smoking (e.g., after waking up, after meals, nothing to do), the presence of someone smoking, stress, etc. Furthermore, patients with psychological dependence associate their pleasant experiences with smoking, and a series of such experiences enhances the psychological conditioned response to

smoking. Psychological dependence is treated with psychotherapy including behavioral therapy.

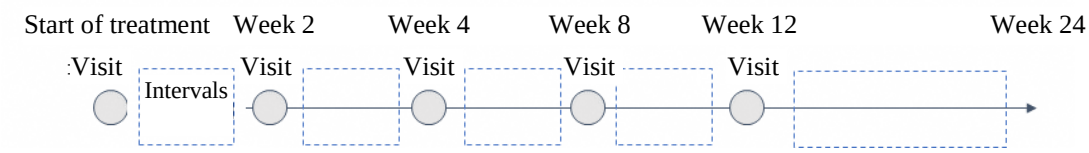
The current smoking cessation treatment begins with a questionnaire, score-based test, etc. at the first visit. Patients who are diagnosed to have nicotine dependence will receive smoking cessation guidance based on the standard treatment program according to the Standard Procedure. The standard smoking cessation treatment program typically consists of a total of 5 visits over a 12-week treatment period, including the first visit, Weeks 2, 4, 8, and 12 visits. Treating physicians prescribe a smoking cessation drug, commonly, varenicline or nicotine patch, both of which are approved ethical drugs.[2]

During the standard smoking cessation treatment program, physicians provide intervention only at visits. During intervals between visits, patients are likely to start smoking again due to stress on daily life, temptations, etc., which are in many cases difficult to cope with by them and their families alone. As a solution, Voxiva, Inc., a US-based company, developed "Text2Quit,"a program that encourages appropriate behaviors via mobile phone text-messaging during inter-visit periods. Text2Quit is a program, designed in accordance with the U.S. Public Health Service Clinical Practice Guidelines, etc., allowing interactive messaging between the user and the program. Text2Quit is a non-medical device and is not intended to be used with smoking cessation treatment on an outpatient basis. From 2011 to 2013, a randomized comparative study on Text2Quit was conducted in 503 smokers for comparison with smoking cessation guidance materials. The continuous abstinence rate (CAR), the primary endpoint of the study at 6 months post-enrollment, was 11.1% in the intervention group and 5.0% in the control group. This outcome suggests that the text messaging program for smoking cessation support is more effective than the provision of conventional smoking cessation guidance materials.[3] The effect of smoking cessation treatment in combination with counseling was evaluated in the meta-analysis of clinical research in 2008. The result indicated that the combination of pharmacotherapy with counseling improves smoking cessation success rate as the number of counseling session increases.[4] Based on these findings, the applicant considered that the provision of therapeutic intervention outside clinic visits would improve the smoking cessation success rate in patients with psychological dependence.

Furthermore, data from the clinical studies for smoking cessation treatment drugs showed a decline in point prevalence abstinence rates during Weeks 13 to 24.[5,6] The applicant, therefore, has prospect that there is a clinical need for continuous support for smoking cessation during this period.

Based on the above, the CASC system was developed as an aid in smoking cessation treatment, for the purpose of providing therapeutic intervention not only during inter-visit periods in the standard smoking cessation treatment program but also during the post-program period up to Week 24 (Figure 4). The concept of CASC system is consistent with that of the standard smoking cessation treatment program, through which patients gain accurate knowledge and are encouraged for behavior change. Furthermore, in the standard smoking cessation treatment program, exhaled CO level is an objective indicator of the patient's smoking status. The CASC system is expected to support physicians in diagnostic decision making and diagnosis-based treatment planning according to the exhaled CO levels measured at home with the CO checker, a component of the system.

Standard smoking cessation treatment program



Treatment program combined with the CASC system

Figure 4. Standard smoking cessation treatment program and treatment intervention by the CASC system

1.(2) Use in foreign countries

The CASC system has not been approved or certified overseas.

2. Design and Development

2.(1) Performance and safety specifications

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

The proposed performance specifications of the patient app and doctor app include the following functions: smoking cessation diary, treatment program, action management, chat, patient self-management display, support, patient user information management, patient data display, diary linked with the doctor app, treatment program linked with the physician, and treatment assistance for the physician. The proposed performance specifications of the CO checker comprise measurement range and measurement accuracy.

The proposed safety specifications of the patient app and doctor app comprise the software life cycle process. The proposed safety specifications of the CO checker comprise electrical safety, electromagnetic compatibility, mechanical safety, biological safety, and software life cycle process.

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

PMDA reviewed the data relating to the performance and safety specifications proposed by the applicant and concluded that there were no particular problems with the specifications.

2.(2) Safety specifications

2.(2).1) Electrical safety and electromagnetic compatibility

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

The applicant submitted data relating to the electrical safety and electromagnetic compatibility of the CO checker: results of the studies conducted using the CO checker in accordance with the Japanese Industrial Standard (JIS) T0601-1:2012 + amendment: 2014 Medical electrical equipment – Part 1: General requirements for basic safety and essential performance and JIS T0601-1-2:2012 Medical electrical equipment – Part 1-2: General requirements for safety –

Electromagnetic compatibility – Requirements and tests. The results indicated that the CO checker conforms to the standards, which demonstrated the electrical safety and electromagnetic compatibility of the device.

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

PMDA reviewed the data relating to the electrical safety and electromagnetic compatibility and concluded that there were no particular problems.

2.(2).2) Biological safety

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

The mouthpiece of the CO checker, which comes in contact with the labial mucosa, is made of a material commonly used in the medical field. Considering that the biological safety of the component has been well established, the submission of biological safety results was omitted.

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

PMDA concluded that there were no particular problems with omitting the submission of data relating to biological safety.

2.(2).3) Mechanical safety

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

The data indicating the conformance of the CO checker to the electrical safety standard (JIS T0601-1:2012 + amendment: 2014) also include the results of the mechanical safety evaluation of the CO checker. The CO checker, which is provided to the patient by the physician, is intended for use at home; and therefore, the data submitted include the results of proven accuracy of CO measurement maintained under expected mechanical stresses in daily life (dropping, vibration, impact, high temperature, low temperature, high humidity, and low humidity).

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

PMDA reviewed the data relating to mechanical safety and concluded that there were no particular problems.

2.(2).4) Stability and durability

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

Submission of stability data relating to the shelf life specification was omitted according to the "Handling of stability studies relating to the determination of the shelf life in the application for marketing approval (certification) of medical devices" (PFSB/ELD/OMDE Notification No.1227-5, dated December 27, 2012). The applicant declared itself in written form that the product shelf life was specified based on the required stability evaluation.

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

PMDA concluded that there were no particular problems with the omission of stability and durability data submission.

2.(3) Performance

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

The applicant submitted data relating to the performance of the patient app and doctor app, i.e.,

evaluation data regarding appropriate performance of the functions. The applicant also submitted data relating to the performance of the CO checker, i.e., the measurement accuracy of exhaled CO levels.

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

The CO checker may not measure exhaled CO level accurately after consumption of alcohol or dairy products, etc. PMDA instructed the applicant to take necessary measures, such as information provision in the package insert. The applicant accepted the instruction.

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

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the product 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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (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 the CASC system to the Essential Principles.

3.B.(a) PMDA's conclusion on the conformity of the CASC system to Article 1, which stipulates the preconditions for designing medical devices (particularly, the requirements for users such as expected level of technical knowledge and experience, and expected level of education and training to be provided to users):

As mentioned in Section "6.B. (3) Smoking cessation treatment drugs used in combination" and Section "6.B.(4) Patients exclusively using heated tobacco products that do not raise the level of exhaled CO (heated tobacco products)," the identification of eligible patients is critical to ensure the efficacy of the CASC system. PMDA has therefore instructed the applicant to take necessary measures such as information provision in the package insert.

3.B.(b) PMDA's conclusion on the conformity of the CASC system to Article 6, which stipulates the efficacy of medical devices:

As mentioned in Section "6.B. (1) Evaluation of primary endpoint," PMDA concluded that it is beneficial to provide the CASC system to the clinical setting based on the results of the clinical studies on the CASC system.

3.B.(c) PMDA's conclusion on the conformity of the CASC system to Article 10, which stipulates requirements for consideration on measuring functions:

As mentioned in Section "2.(3).B Outline of the review conducted by PMDA," PMDA concluded that validity including the measurement accuracy of the CO checker was demonstrated.

3.B.(d) PMDA's conclusion on the conformity of the CASC system to Article 12, which stipulates requirements for consideration on development life cycle of program-driven medical devices:

As mentioned in Section "2.(1).B Outline of the review conducted by PMDA" and Section "2.(3).B Outline of the review conducted by PMDA," the appropriateness of software life cycle process and the CASC system performance were assessed. PMDA concluded that the requirements are appropriately met.

3.B.(e) PMDA's conclusion on the conformity of the CASC system to Article 16, which stipulates requirements for medical devices intended to be used by general users:

As mentioned in Section "2.(2).3).B Outline of the review conducted by PMDA," measurement accuracy and safety of the CASC system in daily use by general users were assessed. PMDA concluded that the requirements are appropriately met.

3.B.(f) PMDA's conclusion on the conformity of the CASC system to Article 17, which stipulates provision of information to users through the package insert or other means:

As mentioned in Section "2.(3).B Outline of the review conducted by PMDA," the CO checker may not measure exhaled CO level accurately after consumption of alcohol or dairy products, etc. Therefore, PMDA instructed the applicant to take necessary measures, such as information provision using the package insert.

Based on the above, PMDA comprehensively reviewed the conformity of the CASC system to the Essential Principles, and concluded that there were no particular problems.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management implemented and the system and status of implementation in accordance with International Organization for Standardization (ISO) 14971:2012 "Medical devices—Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

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

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data relating to the manufacturing process, which consisted of data relating to the items of test to be conducted during the production.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data relating to the manufacturing process and concluded that there were no particular problems.

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

6.A Summary of the data submitted

The applicant submitted results from a clinical study conducted in Japan.

6.A.(1) Study design

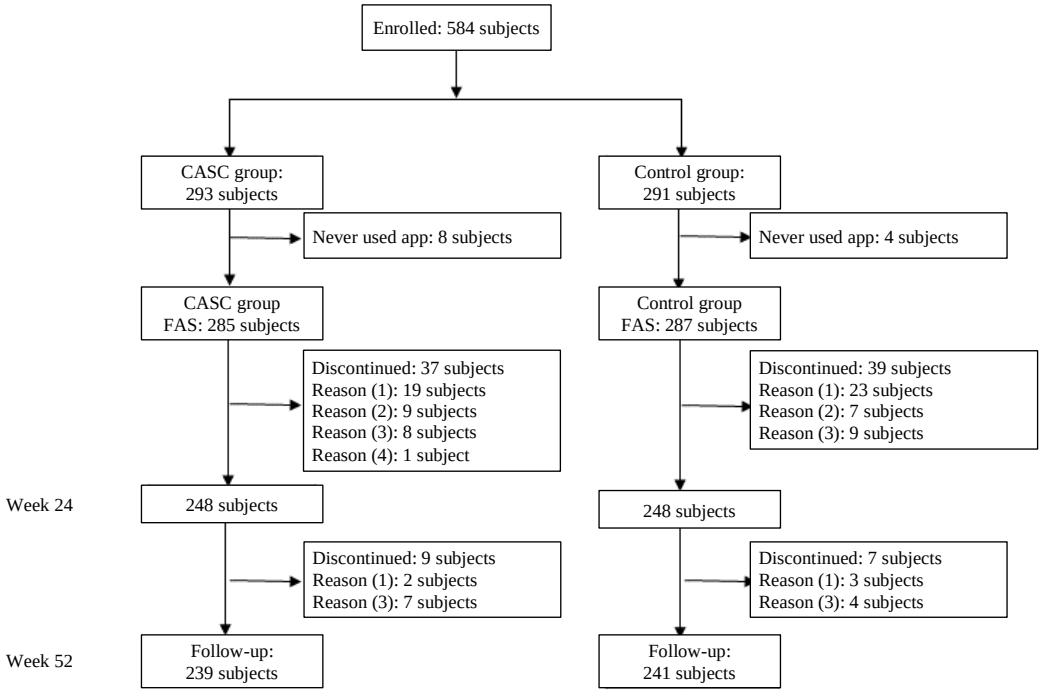
The study was conducted at 31 study centers in Japan from [redacted] (enrollment date of the first subject) to [redacted] (the completion date of the last follow-up) using a randomized, open-label, parallel-group design to evaluate the efficacy and safety of the CASC system in patients with nicotine dependence. Table 2 summarizes the outline of this study. The details of the number of subjects and reasons for discontinuation are shown in Figure 5.

Table 2. Outline of clinical study

Objective	To verify the effectiveness of the CASC system when used in combination with the standard smoking cessation treatment program in patients with nicotine dependence by comparing with the control app.[*1]
Design	Multicenter, randomized, 2-group intervention study
Sample size	Enrollment, 584 subjects (CASC, 293; control, 291) FAS,[*2] 572 subjects (CASC, 285; control, 287)
Number of study centers	31
Inclusion criteria	Patients who meet all the following criteria 1) through 5) 1) Confirmed diagnosis of nicotine dependence based on the Tobacco Dependence Screener (TDS)(≥5 points) 2) Brinkman index of ≥200 (number of cigarettes smoked daily × years of smoking) 3) Hoping to quit smoking immediately 4) Provision of written consent for smoking cessation treatment 5) User of a smartphone (operating system: Android 5.0 or above, iPhone 8.0 or above)
Exclusion criteria	Patients who meet any of the following criteria 1) through 4) 1) Having difficulty participating in the study owing to severe mental illness or other reasons 2) Having difficulty attending follow-up visits for a year since the start of treatment 3) Likely being affected by a smoking cessation treatment drug taken prior to the start of the clinical study 4) Being scheduled to use other smoking cessation support materials or participate in another smoking cessation activity (not limited to smoking cessation treatment), etc.
Primary endpoint	CAR at Weeks 9 to 24
Secondary endpoints	(a) CAR from Weeks 9 to 12 (b) CAR from Weeks 9 to 52 (c) Change in Mood and Physical Symptoms Scale (MPSS) (MPSS total and Urges total) score[7] (d) Change in the 12-item French version of the Tobacco Craving Questionnaire (FTCQ-12) score[8] (e) Change in the score of Kano Test for Social Nicotine Dependence (KTSND)[9] (f) Point prevalence abstinence rates at Weeks 4, 8, 12, 24, and 52 (g) Time to first lapse after the quit date (h) Use status of treatment app (i) Occurrence of malfunctions and adverse events (complications)

[*1] The control app has [redacted] with no functions that may contribute to efficacy. The control app is not used in combination with a CO checker.

[*2] Subjects who were enrolled in the study and received assigned treatment at least once were included in the FAS.



Reason for discontinuation (1): The discontinuation of nicotine dependence treatment was requested by the subject.
Reason for discontinuation (2): Continued smoking cessation was not observed at Week 9 and thereafter, and the continuation of the study was deemed unsuitable by the investigator.
Reason for discontinuation (3): The continuation of study treatment was deemed unsuitable by the investigator for other reasons (e.g., patients were unreachable, judged to have no intention of quitting smoking, or unable to install app).
Reason for discontinuation (4): After starting use of the study device, the patient was found not meeting the inclusion criteria or violating the exclusion criteria.

Figure 5. Number of subjects and reasons for discontinuation

The primary efficacy endpoint was the CAR from Weeks 9 to 24 as an indicator of the superiority of the CASC system. It represents the proportion of subjects who satisfy the following 2 conditions at one time relative to all subjects evaluated:

- Self-reported abstinence continuing from the day following the 4th visit (Week 8 of treatment) to Week 24
- Exhaled CO levels of ≤10 ppm at scheduled visits at Weeks 12 and 24[5,6]

Evaluation methods for the secondary endpoints, (a) CAR from Weeks 9 to 12 and from Weeks 9 to 52 and (b) point prevalence abstinence rates at Weeks 4, 8, 12, 24, and 52 are summarized in the following sections.

6.A.(1).(a) CAR from Weeks 9 to 12 and from Weeks 9 to 52

The CARs from Weeks 9 to 12 and from Weeks 9 to 52, respectively, were defined as the proportion of subjects who satisfy the following conditions at one time relative to all subjects evaluated.

CAR from Weeks 9 to 12

- Self-reported abstinence continuing from the day following the 4th visit (at Week 8 of treatment) to Week 12
- Exhaled CO level of ≤10 ppm at scheduled visit at Week 12

CAR from Weeks 9 to 52

- Self-reported abstinence continuing from the day following the 4th visit (Week 8 of treatment) to Week 52
- Exhaled CO levels of ≤10 ppm at scheduled visits at Weeks 12, 24, and 52

6.A.(1).(b) Point prevalence abstinence rates at Weeks 4, 8, 12, 24, and 52

The abstinence rate at each evaluation timepoint was defined as the proportion of subjects who satisfy the following 2 conditions relative to all subjects evaluated.

- Self-reported abstinence for the 7 days preceding a visit including the day of visit
- Exhaled CO levels of ≤10 ppm measured at visits, evaluation timepoints

In the evaluation of efficacy, treatment discontinuation and deviation were regarded as unsuccessful cases of smoking cessation. Patients who used heated tobacco products during each CAR evaluation period were included in unsuccessful cases of smoking cessation.[ii]

The sample size was determined as 290 subjects per group. In light of the study design allowing the verification of the superiority of the CASC system, when the outcome of the primary endpoint with the CASC system is estimated to be [redacted]%, each group needs to have 287 subjects with a power of 80% and a significance level of 5% (two-sided).

6.A.(2) Patient characteristics

Table 3 shows the characteristics of patients enrolled in the clinical study. There was no statistically significant difference in patient characteristics between the groups.

Table 3. Patient characteristics

	CASC	Control
Age (years) (mean ± standard deviation)	46.5 ± 10.65	45.4 ± 11.54
Sex	Male, 75.8% Female, 24.2%	Male, 73.2% Female, 26.8%
Body weight (kg) (mean ± standard deviation)	68.00 ± 13.530	66.65 ± 13.198
Years of smoking (years) (mean ± standard deviation)	25.6 ± 10.12	25.1 ± 11.23
Number of cigarettes smoked per day (mean ± standard deviation)	19.0 ± 6.19	20.0 ± 7.24
Past smoking cessation treatment (proportion of patients with no past cessation treatment)	83.5% (238/285)	84.0% (241/287)
TDS (mean ± standard deviation)	7.7 ± 1.44	7.8 ± 1.49
BI (mean ± standard deviation)	477 ± 253.65	486 ± 293.75
FTND (mean ± standard deviation)	5.2 ± 2.04	5.3 ± 2.12

[ii] Heated tobacco products contain nicotine.

6.A.(3) Study results

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

The CAR during 16 weeks from Weeks 9 to 24, the primary endpoint, was 63.9% (182 of 285 subjects) in the CASC group and 50.5% (145 of 287 subjects) in the control group. In the logistic regression analysis using type of smoking cessation drug as a covariate, the odds ratio for CAR in the CASC group to the control group and the 95% CI is 1.73 [1.239-2.424], indicating that CAR in the CASC group was significantly higher than that in the control group (P = 0.001). Among subjects who declared being abstinent, none had measured CO levels of >10 ppm at any timepoint.

6.A.(3).2) Secondary efficacy endpoints

The CAR during 4 weeks from Weeks 9 to 12 was 75.4% (215 of 285 subjects) in the CASC group and 66.2% (190 of 287 subjects) in the control group. In the logistic regression analysis using type of smoking cessation drug as a covariate, the odds ratio for CAR in the CASC group to the control group and the 95% CI is 1.57 [1.089-2.267], indicating that CAR in the CASC group was statistically significantly higher than that in the control group (P = 0.016).

The CAR during 44 weeks from Weeks 9 to 52 was 52.3% (149 of 285 subjects) in the CASC group and 41.5% (119 of 287 subjects) in the control group. In the logistic regression analysis using type of smoking cessation drug as a covariate, the odds ratio for CAR in the CASC group to the control group and the 95% CI is 1.55 [1.111-2.155], indicating that CAR in the CASC group statistically significantly higher than that in the control group (P = 0.010).

Point prevalence abstinence rates at Weeks 4, 8, 12, 24, and 52 were 71.6%, 78.6%, 79.3%, 72.3%, and 63.5%, respectively, in the CASC group, and 60.3%, 69.3%, 71.1%, 58.2%, and 49.1%, respectively, in the control group. In the logistic regression analysis using type of smoking cessation drug as a covariate, the odds ratio for the point prevalence abstinence rate at each evaluation timepoint in the CASC group to the control group and the 95% CI was 1.67 (95% CI, 1.173-2.376; P = 0.004) at Week 4; 1.63 (95% CI, 1.113-2.389; P = 0.012) at Week 8; 1.56 (95% CI, 1.062-2.302; P = 0.024) at Week 12; and 1.80 (95% CI, 1.290-2.519; P < 0.001) at Week 52. The point prevalence abstinence rate at each evaluation timepoint in the CASC group was statistically significantly higher than that in the control group. At Week 24, all [redacted] subjects assigned to “no medication” successfully quit smoking, and thus the logistic regression model did not converge.

Comparisons were performed in the covariate-adjusted least squares mean change from baseline in the MPSS total score at Weeks 12 and 24 between the groups. There was a statistically significant decrease in the MPSS score in the CASC group as compared with the control group. For the urge total score, comparisons were performed in the covariate-adjusted least squares mean change from baseline at Weeks 4, 8, 12, 24, and 52 between the groups. The urge score was statistically significantly lower in the CASC group than in the control group.

Comparisons were performed in the covariate-adjusted least squares mean change from baseline in KTSND score at Weeks 8, 12, 24, and 52 between the groups. The KTSND score was statistically significantly lower in the CASC group than in the control group.

Change in FTCQ-12 score was evaluated using general craving score, which is derived by summing all items. Comparisons were performed in the covariate-adjusted least squares mean change from baseline in FTCQ-12 general craving score at Weeks 2, 4, 8, 12, 24, and 52 between the groups. The general craving score was statistically significantly lower in the CASC group than the control group at all the timepoints.

A comparison was performed in the covariate-adjusted least squares mean for time to first lapse after the quit date between the groups. Time to first lapse after the quit date was statistically significantly longer in the CASC group than in the control group.

6.A.(3).3) Use of the CASC system

According to the results of CAR from Weeks 9 to 24, the functions of the CASC system which contributed to the difference in the utilization of the system between successful and unsuccessful quitters were treatment program, action management, smoking cessation diary, and chat functions.

6.A.(3).4) Malfunctions

Among the 584 subjects enrolled, 71 of 293 subjects in the CASC group experienced a total of 85 cases of malfunctions and 43 of 291 subjects in the control group experienced a total of 44 cases. The most common malfunction was display failure (28 cases), followed by data entry failure (5 cases), computation failure (5 cases), and data transmission failure (5 cases). None of the malfunctions were considered to have affected the health condition of the subjects.

6.A.(3).5) Adverse events

The incidences of all adverse events (Table 4) and adverse events with an incidence of ≥1% in either group (Table 5) from the start to the end of study were tabulated. A causal relationship to the CASC system or the control device was ruled out for all events.

Table 4. Incidence of adverse events

Percentage of subjects who developed adverse events	CASC	Control
Mild	54.7% (156/285)	47.4% (136/287)
Moderate	14.0% (40/285)	17.1% (49/287)
Severe	0.7% (2/285)	2.1% (6/287)
Serious	2.8% (8/285)	3.5% (10/287)

Table 5. Adverse events with an incidence of ≥1% in either group

	CASC (n = 285)		Control (n = 287)	
System organ class Preferred term	Number of subjects (%)	Case	Number of subjects (%)	Case
Subjects with ≥1 TEAE[*1]	198 (69.5)	459	191 (66.6)	403
Cardiac disorders	0 (0.0)	0	3 (1.0)	3
Eye disorders	3 (1.1)	3	2 (0.7)	2
Gastrointestinal disorders	91 (31.9)	125	99 (34.5)	129
Nausea	53 (18.6)	62	64 (22.3)	67
Constipation	14 (4.9)	14	16 (5.6)	16
Abdominal discomfort	9 (3.2)	10	6 (2.1)	6
Abdominal pain upper	4 (1.4)	5	7 (2.4)	7
Vomiting	5 (1.8)	8	4 (1.4)	4
Stomatitis	3 (1.1)	3	3 (1.0)	3
Abdominal distension	3 (1.1)	4	2 (0.7)	2
Gastrooesophageal reflux disease	1 (0.4)	1	4 (1.4)	4

Dyspepsia	3 (1.1)	3	1 (0.3)	1
Gastritis	0 (0.0)	0	4 (1.4)	4
General disorders and administration site conditions	11 (3.9)	12	14 (4.9)	14
Malaise	6 (2.1)	7	5 (1.7)	5
Pyrexia	2 (0.7)	2	3 (1.0)	3
Feeling abnormal	1 (0.4)	1	3 (1.0)	3
Hepatobiliary disorders	3 (1.1)	3	2 (0.7)	2
Infections and infestations	97 (34.0)	125	72 (25.1)	96
Viral upper respiratory tract infection	61 (21.4)	68	45 (15.7)	57
Influenza	18 (6.3)	18	10 (3.5)	10
Bronchitis	5 (1.8)	5	4 (1.4)	4
Upper respiratory tract infection	3 (1.1)	3	6 (2.1)	7
Gastroenteritis	7 (2.5)	8	1 (0.3)	1
Pharyngitis	1 (0.4)	1	3 (1.0)	3
Sinusitis	1 (0.4)	1	3 (1.0)	3
Tonsillitis	3 (1.1)	3	0 (0.0)	0
Injury, poisoning and procedural complications	12 (4.2)	13	3 (1.0)	3
Contusion	3 (1.1)	3	0 (0.0)	0
Foot fracture	3 (1.1)	3	0 (0.0)	0
Investigations	15 (5.3)	16	9 (3.1)	9
Weight increased	12 (4.2)	13	7 (2.4)	7
Metabolism and nutritional disorders	10 (3.5)	11	7 (2.4)	7
Diabetes mellitus	6 (2.1)	6	1 (0.3)	1
Musculoskeletal and connective tissue disorders	20 (7.0)	28	7 (2.4)	10
Back pain	5 (1.8)	6	4 (1.4)	4
Musculoskeletal stiffness	3 (1.1)	3	1 (0.3)	1
Osteoarthritis	3 (1.1)	3	0 (0.0)	0
Nervous system disorders	33 (11.6)	41	44 (15.3)	47
Headache	15 (5.3)	15	15 (5.2)	15
Somnolence	10 (3.5)	10	17 (5.9)	18
Dizziness	2 (0.7)	3	6 (2.1)	6
Psychiatric disorders	21 (7.4)	23	19 (6.6)	21
Insomnia	14 (4.9)	14	9 (3.1)	9
Abnormal dreams	2 (0.7)	2	3 (1.0)	3
Nightmare	3 (1.1)	3	2 (0.7)	2
Renal and urinary disorders	0 (0.0)	0	3 (1.0)	3
Reproductive system and breast disorders	0 (0.0)	0	4 (1.4)	4
Respiratory, thoracic and mediastinal disorders	18 (6.3)	20	16 (5.6)	17
Asthma	3 (1.1)	3	5 (1.7)	5
Upper respiratory tract inflammation	6 (2.1)	6	0 (0.0)	0
Cough	3 (1.1)	3	2 (0.7)	2
Skin and subcutaneous tissue disorders	25 (8.8)	26	23 (8.0)	26
Dermatitis contact	8 (2.8)	9	9 (3.1)	10
Pruritus	5 (1.8)	5	6 (2.1)	6
Erythema	3 (1.1)	3	2 (0.7)	2
Rash	3 (1.1)	3	1 (0.3)	1
Vascular disorders	6 (2.1)	7	7 (2.4)	7
Hypertension	5 (1.8)	6	6 (2.1)	6

[*1] TEAE = Treatment-emergent adverse event.

TEAEs were sorted by internationally agreed order of SOC alphabetically, and sorted by PT decreasing frequency of total

MedDRA Version 20.0 was used to code adverse events.

6.B Outline of the review conducted by PMDA

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

6.B.(1) Evaluation of primary endpoint

The applicant's explanation about the justification for selection of CAR from Weeks 9 to 24 as the primary endpoint:

The CASC system was developed in the expectation that treatment intervention provided from the start through Week 24 of the standard treatment program would promote the continuation of the smoking cessation treatment from Weeks 13 to 24. Success in a smoking cessation treatment of patients with nicotine dependence should preferably be assessed over as long period as possible. In the clinical study of varenicline, an approved ethical drug for smoking cessation treatment, the primary endpoint was CAR from Weeks 9 to 12. Accordingly, by reference to the primary endpoint used in the study on varenicline, a CAR for a relatively longer period, Week 9 to 24, would be a reasonable endpoint for the study on the CASC system. While the standard smoking cessation treatment program ends at Week 12, it was decided that the physicians were required to check the smoking cessation status of their patients at the Week 24 visit.

PMDA's view on the efficacy of the CASC system:
The primary endpoint of the study was CAR as with the study on varenicline, which is the appropriate indicator for the evaluation of the CASC system. The CASC system used in the post-marketing setting may not show equal efficacy to that in the study as indicated by the CAR up to Week 24, as per the directions for use, depending on whether physicians monitor patients' smoking status, if smoking status monitoring by physicians up to Week 24 is not required in the directions for use. Nevertheless, the directions for use proposed in the submitted application are consistent with those in the study. The proposed CAR evaluation period is considered reasonable. Given these, the primary endpoint is appropriate.

The sample size for this study was determined based on the estimated difference in CAR in Weeks 9 to 24 between the CASC group and the control group of [redacted]%. The results showed that the difference in CAR in Weeks 9 to 24 between the CASC group and the control group was 13.4%, which is a statistically significant difference from the control group, and the results demonstrated the efficacy of the CASC system.

6.B.(2) Justification for the use of the control group results for evaluation
The standard smoking cessation treatment program encourages record keeping on smoking cessation activities in diary, etc. According to the protocol of this study, subjects in the CASC group recorded their smoking cessation activities using the smoking cessation diary function. However, there are no available data of subjects in the control group indicating that record keeping was practiced during the standard smoking cessation treatment program, and consequently, to what extent subjects in the control group actually engaged in record keeping as compared with the CASC group remains unknown. Because of the unblinded design of the study, the subjects in the control group naturally knew that they were provided with the control app would not contribute to the treatment. Therefore, subjects assigned to the control group could have been less motivated.

PMDA, in order to clarify whether a low use-rate of smoking cessation diary or decreased motivation in the control group led to the lower CAR than that in the standard smoking cessation treatment program, asked the applicant whether the CAR in the control group is comparable to or higher than that achieved in the standard smoking cessation treatment program currently implemented in the clinical setting.

The applicant's explanation:

Table 6 shows CARs in patients who received nicotine dependence treatment under the national health insurance system (FY2007, 2009, and 2017 reports for "Survey on the Actual Status of Smoking Cessation Rate in Medical Institutions Calculating Insurance Fee for Nicotine Dependence Management" by the Central Social Insurance Medical Council, Ministry of Health, Labour and Welfare [MHLW]). The CARs in the control group are higher than those extracted from the survey data.

PMDA's view:
Although it is not possible to compare the CARs in the control group with those in the subjects who kept a smoking cessation diary every day in usual treatment, the CARs in the control group in this study are higher than those achieved in the standard smoking cessation treatment program currently underway in the clinical setting. Therefore, there are no particular problems with using the results of the control group for evaluation.

Table 6. CARs from FY2007, 2009, and 2017 reports for "Survey on the Actual Status of Smoking Cessation Rate in Medical Institutions Calculating Insurance Fee for Nicotine Dependence Management"

	CAR Weeks 9-12	CAR Weeks 9-24	CAR Weeks 9-52
Control group in the study	66.2% (190/287)	50.5% (145/287)	41.5% (119/287)
FY2007 survey by Central Social Insurance Medical Council	54.1%[*1] (1377/2546)	40.8%[*2] (1040/2546)	32.6%[*3] (830/2546)
FY2009 survey by Central Social Insurance Medical Council	56.1%[*1] (1946/3471)	—	29.7%[*3] (1030/3471)
FY 2017 survey by Central Social Insurance Medical Council	58.3%[*1] (763/1308)	—	27.3%[*3] (357/1308)

[*1] Among patients who completed smoking cessation treatment in 1 to 4 visits, those who maintained smoking abstinence at the end of treatment were regarded as maintaining "continuous abstinence." Among patients who completed 5 visits of smoking cessation treatment, those who continued to maintain smoking abstinence for 4 weeks were regarded as maintaining "continuous abstinence."

[*2] Patients who continued to maintain smoking abstinence for 4 weeks at 3 months after the completion of guidance were regarded as maintaining "continuous abstinence."

[*3] Patients who continued to maintain smoking abstinence for 4 weeks at 9 months after the completion of guidance were regarded as maintaining "continuous abstinence."

6.B.(3) Smoking cessation treatment drugs used in combination

6.B.(3).1) Patients who use [redacted] in combination

Table 7 shows the CAR at Weeks 9 to 24 in the CASC and control groups of this study by smoking cessation treatment drug used in combination. Among subjects who were using concomitant [redacted], no difference was observed in CAR between the CASC and control groups. PMDA asked the applicant to explain the reason.

The applicant's explanation:
The difference between the CASC system algorithms incorporating the use of varenicline and that incorporating the use of [redacted] is attributable to what advice, etc. to be given to patients who complain of bad health or report about a missed dose, which is specified in accordance with

the Standard Procedure and the package insert. The difference between the algorithms is unlikely to have an impact on psychological effects. Therefore, the results of the study do not directly reflect the system's therapeutic effect.

Table 7. CAR from Weeks 9 to 24 in the CASC and control groups by smoking cessation treatment drug used in combination

	CASC	Control
Varenicline	67.0% (152/227)	50.7% (115/227)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

A subgroup analysis was performed by study center on the smoking cessation treatment drugs. At [redacted] study centers, the percentage of subjects prescribed [redacted] was [redacted], which was markedly higher than the national average of 11.1% and was suggestive of incompliance with the Standard Procedure in terms of the prescription of [redacted]. Investigation was conducted at the [redacted] study centers. At [redacted] study center (Study Center A), [redacted] was as extremely low as [redacted] among non-study participants, and usually [redacted] was used as [redacted] unless strongly requested by patients. As compared with a smoking cessation success rate of 58.3% among the general public (MHLW "FY2016 Report on the special survey on verification of the revision results on reimbursement of medical fees [survey in 2017]"), the smoking cessation success rate at Study Center A is low. When the Standard Procedure was followed, the success rate would not be that low, and therefore Study Center A may not have complied with the Standard Procedure. Furthermore, in terms of [redacted], Study Center A may not have complied with the Standard Procedure, which recommends to determine [redacted].

[redacted] study center (Study Center B) was found to have implemented [redacted], which was considered to have caused [redacted], resulting in the modification of the effect of the CASC system. In addition, [redacted] was prescribed for patients who may have a chance to drive a vehicle at work. Given these, because of the implementation of [redacted] and [redacted], there is a possibility that the Standard Procedure was not followed at Study Center B as well.

Furthermore, in response to a questionnaire distributed to all study centers, [redacted] study centers (including [redacted] of [redacted] study centers mentioned above) answered "[redacted]," suggesting that these study centers "may not have followed the Standard Procedure."

An analysis was performed involving the remaining [redacted] study centers other than Study Centers A and B and the [redacted] study centers that answered "[redacted]" in the questionnaire (a total of [redacted] study centers, because [redacted] study centers fell under both categories). The results indicated that among subjects using concomitant [redacted], the CAR from Weeks 9 to 24 was [redacted] in the CASC group and [redacted] in the control group.

The above results suggest that differences observed in the study can be largely attributed to facility factors, and the algorithm, etc. of the CASC system in terms of the use of varenicline or [redacted] is unlikely to have an impact on treatment efficacy. The efficacy of the CASC system is considered to have been demonstrated regardless of the concomitant drug at [redacted] when as many facility factors as possible were eliminated.

PMDA's view:
Even if the algorithm of the patient app conforms to the Standard Procedure and the package insert, the possibility cannot be denied that the differences between the algorithm incorporating the use of varenicline and that with [redacted] affected the efficacy of the CASC system. The standard for [redacted], criteria for smoking cessation treatment results at study centers, and the prohibition of [redacted], which are mentioned above in the discussion on the subgroup analysis by study center, are not specified in the Standard Procedure. Frequent prescription of [redacted], poor outcomes in previous smoking cessation treatments at [redacted], or the implementation of [redacted] at [redacted] do not adequately explain the incompliance with the Standard Procedure or protocol deviation at Study Centers A and B. Furthermore, at Study Center B, the CAR from Weeks 9 to 24 in patients using [redacted] was [redacted] in the CASC group and [redacted] in the control group, indicating that [redacted] is [redacted] in the CASC group than in the control group. Therefore it is unclear whether the results were due to the effect of [redacted]. At the center that prescribed [redacted] frequently and other centers mentioned by the applicant, both CASC and control groups received similar treatment, which resulted in the similar results. The 2 groups were supposed to show different results, and the applicant's explanation about the similar results in the 2 groups is less than scientifically adequate.

Taken together, the study results did not adequately demonstrated the efficacy of the CASC system used as an adjunct to smoking cessation treatment in patients using concomitant [redacted].

6.B.(3).2) Patients with [redacted]
The efficacy of the CASC system in patients with [redacted] is not clear because of the small number of patients participated in the study as shown in Table 7 ([redacted] subjects in the CASC group and [redacted] subjects in the control group). PMDA asked the applicant to explain whether the CASC system has efficacy in patients with [redacted] as well.

The applicant's explanation:
The CASC system primarily aims to support behavioral therapy through proper knowledge and recognition, thereby promoting behavior change to achieve a good result. Therefore, the target population of the CASC system is not the same as that of intervention with smoking cessation treatment drugs for physical dependence. The effect of CASC system, an intervention for psychological dependence, will not be hindered even [redacted]. In addition, the study also involved patients with [redacted] and demonstrated the efficacy of the CASC system.

PMDA's view:
Even though the CASC system is intended for patients with psychological dependence, the possible impact of the difference between the algorithm reflecting [redacted] or that reflecting [redacted] on the efficacy results cannot be denied. Furthermore, limited data from the small number of study participants precludes justification of the efficacy. The efficacy of the CASC system remains unclear in 1) patients who use concomitant [redacted] and 2) patients [redacted], and therefore it is not appropriate to include these patients in the intended treatment population.

PMDA asked the applicant to explain their view of the above issue.

The applicant' explanation:
In response to the study results, [redacted] of the patient and doctor apps related to 1) patients who use concomitant [redacted] and 2) patients [redacted] will be removed, and the specification that the algorithm of the CASC system is based on the concomitant use of the smoking cessation drug, i.e., varenicline will be added. This information will be disseminated via the package insert.

PMDA concluded that there were no problems with the applicant's explanation.

6.B.(4) Patients exclusively using heated tobacco products that do not raise the level of exhaled CO (heated tobacco products)

PMDA asked the applicant to explain whether patients exclusively using heated tobacco products are included in the intended treatment population for the CASC system.

The applicant's explanation:
Although patients using only heated tobacco products were not included in the study, the CASC system is expected to have efficacy in patients with nicotine dependence who are using heated tobacco products as well. Therefore, patients exclusively using heated tobacco products are also eligible for use of the CASC system.

PMDA's view:
The CASC system allows physicians to check the exhaled CO levels of the patient measured with the CO checker. Monitoring of CO levels by the physician is effective to some extent in supporting continuous abstinence. However, heated tobacco products, which contain tobacco leaves, do not reach a temperature that can combust the tobacco leaves, thus do not generate CO in exhaled breath. There is no point in measuring exhaled CO levels, although which will be checked by the physician and the patient. This suggests that CO level monitoring by the physician will be no longer effective on continuous abstinence and that the CASC system may not have equal efficacy in users of heated tobacco products in comparison to that shown in the study.

PMDA asked the applicant to explain the rationale for the efficacy of the CASC system in patients who are exclusively using heated tobacco products.

The applicant's explanation:
The CO checker assists physicians in diagnostic decision making relating to smoking cessation

treatment. The device is intended to aid physicians in treatment planning according to the diagnosis made based on home-measured exhaled CO levels and self-reported smoking cessation activities of patients. As described below, the CO checker does not contribute to continuous abstinence, and therefore, the clinical benefit of the CASC system will be maintained even when it is used by users of heated tobacco products.

- There is evidence that CO checker does not contribute to continuous abstinence in a systematic review article.[10]
- A logistic regression analysis was performed in the study using the exhaled CO level measurement as a variable. The odds ratio of smoking cessation success at Week 24 was [redacted] (95% CI, [redacted]; *P* = [redacted]) for an increase in the number of measurement using the CO checker by 1SD ([redacted] times), indicating that exhaled CO level measurement itself does not contribute to successful smoking cessation.
- In this study, the exhaled CO level measurement rate was [redacted]% in subjects who succeeded in continuous abstinence from Weeks 9 to 24, and [redacted]% in subjects who failed to quit smoking, indicating that the exhaled CO level measurement rate of successful quitters was slightly lower.
- In this study, there was no trend toward increasing smoking cessation success rate with increased number of exhaled CO level measurements.

Although the study excluded patients who were exclusively using heated tobacco products, [redacted] subjects in the CACS group and [redacted] subjects in the control group were using both heated tobacco products and paper-wrapped cigarettes. Among these subjects, the CAR from Weeks 9 to 24 was [redacted] in the CASC group and [redacted] in the control group. In these subjects as well, although a few in number, added therapeutic effect was observed, which is consistent with the view that the CASC system has efficacy in patients using heated tobacco products.

PMDA's view:
The systematic review article referred to by the applicant does not mention continuous abstinence achieved during treatment in conjunction with once-daily exhaled CO level measurement at home, such as that with the CO checker. This does not necessarily mean that daily exhaled CO level measurement using the CO checker does not contribute to continuous abstinence.

In this study, there were only [redacted] subjects who never used the CO checker. The applicant has explained the difference in the number of measurements of exhaled CO level and the difference in the exhaled CO level measurement rates among patients who underwent the measurement. However, the effect of exhaled CO level measurement on CAR in patients who never underwent the measurement remains unknown. Thus, it is unclear whether the CASC system would contribute to the CAR as in the study if it did not have the function allowing physicians to check the exhaled CO, and this consequently precludes a conclusion on whether the CASC system be equally effective in those who are exclusively using heated tobacco products as compared to that used in the study.

Among the patients who were using both types, the consumption rates for heated tobacco products and paper-wrapped cigarettes are unknown. Given unclear effect of exhaled CO levels and the small number of subjects, the efficacy of the CASC system in patients who are exclusively using heated tobacco products cannot be clearly ascertained based on the results in patients who are

using both types of cigarettes.

Given these observations, it is not considered appropriate to include patients who are exclusively using heated tobacco products that do not raise exhaled CO level in the intended treatment population for the CASC system. PMDA asked the applicant to explain this point.

The applicant's response:
Users of heated tobacco products that do not raise the level of exhaled CO will be exclude from the intended treatment population for the CASC system, and thus the "Direction for Use" section will specify that the patient's smoking status needs to be confirmed prior to the treatment, which will be communicated via the package insert.

PMDA concluded that there were no problems with the applicant's proposed action.

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

Use results-based efficacy evaluation of the CASC system is unnecessary for the following reasons: the study demonstrated the clinical efficacy of the system; the criteria for the selection of study centers and inclusion criteria for participants were determined based on the calculation standard for the nicotine dependence management fee referred in clinical practice, indicating that the study was conducted in situations similar to the actual setting. Similarly, a use-results evaluation on safety is also unnecessary because the study was conducted in a setting similar to actual setting and the safety of the patient and doctor apps of the CASC system is considered to have been well verified.

7.B Outline of the review conducted by PMDA

The views on the safety of the CASC system are presented in "2.(2) Safety specifications." As mentioned in "6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare," there were no adverse events of concern, and the risk associated with the system is extremely low. Therefore, a post-marketing use-results evaluation is unlikely to identify new safety concerns.

The criteria for the selection of study centers and inclusion criteria for study participants have been determined based on the calculation standard for the nicotine dependence management fee referred in clinical practice. Consequently, the study was conducted in a near-real setting, except for the exclusion of users of heated tobacco products alone. Therefore, taking into account that patients who are using heated tobacco products alone are excluded from the intended treatment population, the efficacy of the CASC system in the intended treatment population was verified.

Taking into account comments from the Expert Discussion, PMDA concluded that use-results evaluation is not necessary for the CASC system given the unlikely emergence of new issues to be investigated, and thus the need for a use-results evaluation is low.

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 compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960). 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.

PMDA's conclusion concerning the results of the on-site GCP inspection

The medical device application data were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960). On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

The CASC system is a smoking cessation treatment support system intended for patients with nicotine dependence. The key issues in the product review were (1) the evaluation of primary endpoint; (2) justification for the use of the control data for evaluation; (3) smoking cessation treatment drugs used in combination; and (4) patients who are exclusively using heated tobacco products. Taking into account the comments from the Expert Discussion, PMDA has reached the conclusions below.

(1) Evaluation of primary endpoint

The sample size was determined on the assumption that the difference in CAR in Weeks 9 to 24 between the CASC group and the control group be [redacted]%. The results showed that the difference in CAR in Weeks 9 to 24 between the groups was 13.4%, which is statistically significant as compared with the control group. PMDA therefore concluded that the results had demonstrated the efficacy of the CASC system.

(2) Justification for the use of the control group results for evaluation

The standard smoking cessation treatment program recommends record keeping on smoking cessation activities in the diary. However, the applicant did not document the diaries implemented in the standard smoking cessation treatment program, and as a result, to what extent diary keeping was implemented in the control group remains unknown. However, the CAR in the control group is higher than the CAR data in patients who received nicotine dependence treatment under the national health insurance system (FY2007, 2009, and 2017 reports for "Survey on the Actual Status of Smoking Cessation Rate in Medical Institutions Calculating Insurance Fee for Nicotine Dependence Management" by the Central Social Insurance Medical Council). The results indicate that the CAR in the control group in this study is higher than the CAR achieved in the standard smoking cessation treatment program available in the current clinical setting. PMDA therefore

concluded that the comparison with the control group has significance.

(3) Smoking cessation treatment drugs used in combination

The efficacy of the CASC system in patients using concomitant [redacted] and patients [redacted] was not clear in this study because of no difference shown in the CAR in Weeks 9 to 24 between the CASC group and the control group. Therefore, PMDA concluded that the intended treatment population and related functions should be strictly defined and informed via the package insert.

(4) Patients who are exclusively using heated tobacco products

The study results do not clearly explain whether the CASC system, if without the exhaled CO monitoring function for physicians, would achieve as high CAR as that achieved in the study. Consequently, it is not clear whether the CASC system is equally effective in those who are exclusively using heated tobacco products as it was in the study. Therefore, patients who are exclusively using heated tobacco products, which do not raise the level of exhaled CO, should not be included in the intended treatment population for the system.

Based on the above discussions, patients who are using heated tobacco products that do not raise the level of exhaled CO will be excluded from the intended treatment population for the CASC system. PMDA concluded that the confirmation of the patient's smoking status should be required prior to the use of product, and this should be informed via the package insert.

As a result of the review, PMDA concluded that the CASC system may be approved for the intended use shown below.

Intended Use

Assistance in smoking cessation treatment of patients with nicotine dependence

The product is not classified as a biological product or a specified biological product.

This application should be subject to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

References Cited

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