February 6, 2025
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Program 2, Software for treatment of diseases
Term Name	Supporting software for treatment of alcohol dependence
Brand Name	CureApp AUD A Digital Therapeutic to Reduce Alcohol Consumption
Applicant	CureApp, Inc.
Date of Application	March 21, 2024 (Application for marketing approval)

Results of Deliberation

In its meeting held on February 6, 2025, the Subcommittee on Software as a Medical Device of the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product should be approved 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

January 28, 2025
Pharmaceuticals and Medical Devices Agency

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

Classification	Program 2, Software for treatment of diseases
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Applicant	CureApp, Inc.
Date of Application	March 21, 2024
Items Warranting Special Mention	
Reviewing Office	Office of Software as a Medical Device

Review Results

January 28, 2025

Classification	Program 2, Software for treatment of diseases
Term Name	Supporting software for treatment of alcohol dependence
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Applicant	CureApp, Inc.
Date of Application	March 21, 2024

Results of Review

The "CureApp AUD A Digital Therapeutic to Reduce Alcohol Consumption" (hereinafter referred to as the CureApp AUD App) is a software program for patients with alcohol dependence for whom alcohol reduction treatment is indicated. It consists of a software application for patients to be installed on general-purpose mobile devices such as smartphones, and a software application for physicians. The CureApp AUD App is used in combination with conventional treatment for alcohol consumption reduction, enables the patient and the physician to share a treatment goal, and provides personalized psychosocial treatment.

The applicant submitted non-clinical data supporting the performance and the software development life cycle process of the CureApp AUD App. The data revealed no particular problems.

Also submitted were clinical data of the CureApp AUD App from a prospective, multicenter, parallel-group study conducted in Japan in patients with alcohol dependence whose goal was to reduce their alcohol consumption (hereinafter referred to as Study ALM-003).

The change from baseline in the number of heavy drinking days at Week 12, the primary endpoint, was −12.237 ± 0.698 days/4 weeks in the intervention group and −9.453 ± 0.678 days/4 weeks in the control group. The difference in adjusted mean between the groups (lower bound to upper bound of the 95% confidence interval [CI]) was −2.785 days/4 weeks (−4.666 days/4 weeks to −0.904 days/4 weeks), indicating a significant reduction in the intervention group compared to the control group ($P = 0.0038$). The results also demonstrated trends toward improvement in the intervention group compared to control for secondary endpoints including "change from baseline in total alcohol consumption at Week 12 and Week 24," and "Response Low Drinking Risk Level

(at Week 12 and Week 24)," "changes from baseline in blood test items at Week 12 and Week 24)."

The results for the safety endpoint, "adverse events and malfunctions," were as follows: 73 adverse events occurred in 46 subjects (32.9%) in the intervention group and 75 adverse events in 48 subjects (33.6%) in the control group. A causal relationship to the CureApp AUD App was ruled out for all events reported in the intervention group. In the intervention group, 26 events of malfunction occurred in 24 subjects (17.1%). All these events were unpredictable malfunctions and were unlikely to do harm to health. Based on the results of the safety endpoint, it was concluded that there are no particular safety concerns associated with the CureApp AUD App.

The self-monitoring and goal management functions of the CureApp AUD App assist in continual psychosocial treatment and are essential for continuous alcohol consumption reduction. Because Study ALM-003 revealed no particular safety concerns in the long-term use of these functions, there is no need to limit treatment duration with the CureApp AUD App.

Study ALM-003 demonstrated a certain level of efficacy and safety of the CureApp AUD App in supporting psychosocial treatment in accordance with the procedures in the "Pocket Edition of the Manual of Treatment for Reduced Drinking, the first edition" [in Japanese] for patients with alcohol dependence for whom alcohol reduction treatment is indicated. The CureApp AUD App should be, therefore, recognized as a medical device that assists in psychosocial treatment.

Based on the review, PMDA concluded that the CureApp AUD App may be approved for the intended use shown below, and that the application should be deliberated at the Subcommittee on Software as a Medical Device.

Intended Use

Aid in the treatment for alcohol consumption reduction in patients with alcohol dependence

Review Report

January 28, 2025

Product for Review	
Classification	Program 2, Software for Treatment of Diseases
Term Name	Supporting software for treatment of alcohol dependence
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Proposed Intended Use	Aid in the treatment in patients with alcohol dependence

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List of Abbreviations

AUD	Alcohol Use Disorders
BMI	Body Mass Index
CIWA-Ar	The revised clinical institute withdrawal assessment for alcohol scale
DRL	Drinking Risk Level
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
FAS	Full analysis set
HDD	Heavy Drinking Day
ICD-10	The tenth revision of the International Statistical Classification of Diseases and Related Health Problems
ISO	International Organization for Standardization
MCID	Minimally Clinically Important Difference
PPS	Per protocol set
MMRM	mixed-effects models for repeated measures
RSDRL	Response Shift Drinking Risk Level
SAF	Safety Analysis Set
TAC	Total Alcohol Consumption
TLFB	Timeline Follow Back
WHO	World Health Organization

I. Product Overview

The "CureApp AUD A Digital Therapeutic to Reduce Alcohol Consumption" (hereinafter referred to as the CureApp AUD App) is a software program for patients with alcohol dependence for whom alcohol reduction treatment is indicated. It consists of a software application for patients, which is to be installed on general-purpose mobile devices such as smartphones ("patient app"), and a software application for physicians ("doctor app") that allows monitoring of patients' daily condition based on data from the patient app through a web browser on a general-purpose terminal unit. The doctor app displays patient data obtained from the patient app and helps set a goal in drinking behavior. The CureApp AUD App allows the patient to share their goal with the physician, and encourages to make behavioral change in daily life through learning about and experiencing psychosocial treatment. In this way, the CureApp AUD App assists in psychosocial treatment aiming at alcohol reduction. The CureApp AUD App is intended for use only under the supervision of a physician. For a patient who has stopped visiting their physician and is no longer under supervision for a long time, even when the treatment with the CureApp AUD App continues, the physician will suspend the use of the patient app through [redacted] so that the patient will have no access to it.

According to the "Guide for Diagnosis and Treatment of Alcohol Dependence in Accordance with the New Diagnostic and Treatment Guidelines for Alcohol and Drug Use Disorders, first edition"[1] (hereinafter referred to as the "Diagnostic and Treatment Guide"), the treatment of alcohol dependence primarily focuses on psychosocial treatment. Physicians offer psychosocial treatment at hospitals, but they have difficulty giving therapeutic guidance to patients on a daily basis. The CureApp AUD App helps patients learn about and experience psychosocial treatment not only as outpatients but also through the patient app, which aggregates patients' daily data and helps physicians and other healthcare professionals to have clearer understanding of patients' conditions at visits. Figure 1 summarizes the treatment algorithm of the CureApp AUD App.

Item	Description
Rectangle with rounded corners (gray)	Functions described in the next section
Arrow (solid line)	Link between functions

Arrow (dashed line)	Link with information entered by patient

Figure 1. Summary of treatment algorithm

The functions of the patient app and the doctor app are summarized as follows. The content of the patient app has been developed in view of [redacted] of the psychosocial treatment for alcohol dependence. Based on the data and results of activities entered by the patient, the app personalizes activities that should be added as routine practices to propose to the patient. Table 1 shows the main functions of the patient app.

Table 1. Main functions of the patient app

Function	Description
Treatment program function	[redacted]
Goal management function	
Self-monitoring function	
Withdrawal symptom detection function	
Consultation diary	
"My data" function	
Patient user information management function	

The doctor app provides the physician with patient information obtained via the patient app, and assists in patient guidance. Physicians can check the patient information, [redacted], and [redacted]. Table 2 shows the functions of the doctor app.

Table 2. Functions of the doctor app

Function	Description
Psychoeducational function	[redacted]
Personalized normative feedback function	

[redacted]

Function	Description
Goal management function	[redacted]
Detailed patient data function	

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 present application and the applicant's response to inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. The expert advisors present during the Expert Discussion on the CureApp AUD App declared that they did not fall under Item 5 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

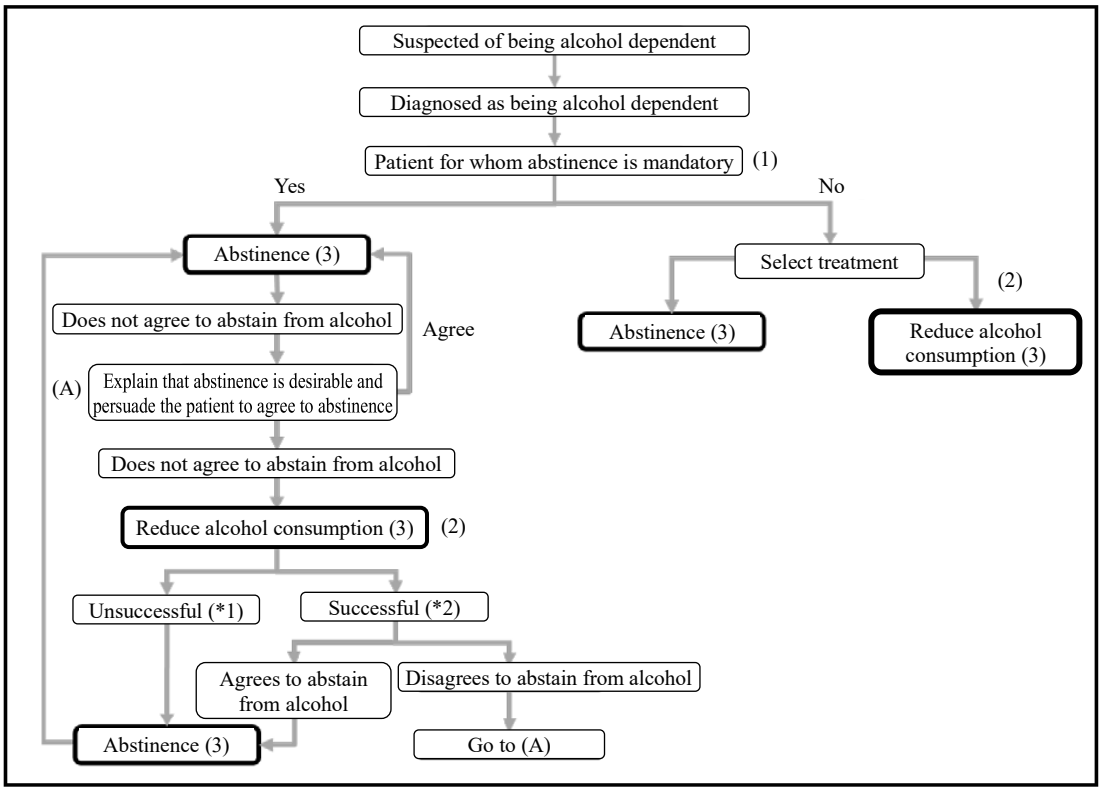
1. History of Development, Use in Foreign Countries, and Other Information

1.(1) History of development

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

In Japan, there are approximately 1.07 million people[2] who are dependent on alcohol. The Basic Act on Measures against Alcohol-related Harm was established in 2013, and the "Alcohol consumption guidelines prioritizing health considerations" was released by the Ministry of Health, Labour and Welfare in 2024. There is growing momentum for addressing the health risks associated with alcohol intake. Conversely, there are only approximately 50,000 patients[3] who have received treatment, suggesting that an estimated 1 million or more patients are untreated. The Diagnostic and Treatment Guide states that psychosocial treatment constitutes the main component of treatment for alcohol dependence, while pharmacotherapy plays an auxiliary role in treatment. However, a variety of issues have been raised, which include medical resources such as an insufficient number of specialized healthcare institutions, and factors related to patients, e.g., there are patients who refuse to agree to being referred to specialized healthcare institutions, and patients who have difficulties in clinic visits because of living in a remote area. The Diagnostic and Treatment Guide discusses the needs for early intervention by primary care physicians or internal medicine doctors.

The "New Diagnostic and Treatment Guidelines for Alcohol and Drug Use Disorders"[3] and the Diagnostic and Treatment Guide show that while permanent abstinence is the most stable and comprehensive goal in the treatment of alcohol dependence, it is essential to continue treatment, and not just focus solely on abstinence, in cases where total abstinence has not been achieved. Thus, alcohol consumption reduction can also be regarded a treatment goal (Figure 2).



*1. Including cases where alcohol consumption can be reduced temporarily, but it is becoming more difficult as time passes

*2. Even if alcohol consumption can be reduced, essentially, abstinence is mandatory. Explain that abstinence is desirable, and persuade the patient to agree to abstinence.

(1) Patients for whom abstinence is mandatory	• Patients who require inpatient treatment and/or patients who have serious problems associated with drinking alcohol and difficulties in social and family life • Patients with serious organ impairment and alcohol may precipitate a life-threatening situation • Patients with ongoing alcohol withdrawal symptoms that require immediate medical attention (e.g., hallucinations, seizures, tremor)
(2) Patients with treatment goal of reducing alcohol consumption	• Mild alcohol dependence without clear comorbid conditions. In such cases, reduction in alcohol consumption can be a treatment goal, unless the patient wants to stop drinking or there are other circumstances that require abstinence. • Even in cases where patients should choose treatment with the goal of treatment being abstinence, if the patient refuses to abstain from alcohol, the patient may have an option to start treatment with the goal of reducing alcohol consumption for the time being, in order to avoid the patient dropping out of the program. If the approach of reducing alcohol consumption does not work, switch to abstinence.

Figure 2. Flowchart for diagnosis/selection of treatment option (cited from the Diagnostic and Treatment Guide)

In recent years, there has been a substantial increase across the world in research and development of software as medical devices to assist in psychosocial treatment, etc. via the patient's smartphone, in tackling obstacles such as difficulties in gaining skills and implementation cost. Also in Japan, several software medical devices have been approved. Under such circumstances,

there has been a report on a randomized study[4] in patients with alcohol dependence that demonstrated the effect of computer-based intervention greater than that of psychologist-delivered face-to-face intervention. The applicant decided to develop the CureApp AUD App, which comprises of the doctor app that monitors patients in their everyday lives outside the clinic and the patient app that assists in psychosocial treatment for alcohol consumption reduction.

1.(2) Use in and outside Japan

The CureApp AUD App is a domestically-developed product and has not been used in other countries.

2. Design and Development

2.(1) Performance and safety specifications

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

The proposed performance specifications of the CureApp AUD App include the following functions of the patient app and doctor app: capable of properly implementing the functions related to learning, implementation of action, and motivation (for the patient app); and a series of operations such as displaying information to be used as an aid for guiding patients (for the doctor app).

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

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

2.(2) Safety specifications

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

In terms of safety, it has been confirmed that the CureApp AUD App meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as “the Essential Principles”) (MHLW Public Notice No. 122, 2005). No specifications have been proposed. Regarding the conformity to the Essential Principles, the applicant submitted data by which conformity to the JIS T 2304:2017 was evaluated in terms of the software life cycle process, separately from the document containing a declaration of conformity described later in Section II.3.

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

PMDA reviewed the data relating to the software life cycle process, and concluded that there were no particular problems.

2.(3) Performance

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

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

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

PMDA reviewed the data submitted by the applicant to evaluate if the functions have been properly implemented, 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 the CureApp AUD App meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the CureApp AUD App to the Essential Principles as shown below.

(1) PMDA's conclusion on the conformity of the CureApp AUD App 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 described later in Section "6.B Outline of the review conducted by PMDA," to ensure the efficacy and safety of the CureApp AUD App, it is important that users are fully informed on the correct usage so that the CureApp AUD App is used in accordance with the appropriate clinical positioning. PMDA therefore instructed the applicant to review the intended use of the CureApp AUD App, and take necessary measures to provide information, e.g., releasing information on precautions, or including such information in the package insert and other materials (Information on Precautions, etc.).

(2) PMDA's conclusion on the conformity of the CureApp AUD App to Article 3, which stipulates the performance and function of medical devices, and Article 6, which stipulates the efficacy of medical devices:
As described later in Section "6.B Outline of the review conducted by PMDA," the clinical study demonstrated that the CureApp AUD App has a certain level of clinically meaningful efficacy in alcohol consumption reduction. PMDA concluded that there were no problems with conformity to Articles 3 and 6.

(3) PMDA's conclusion on the conformity of the CureApp AUD App to Article 12, which stipulates requirements for consideration on program-driven medical devices:
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," the appropriateness of the software life cycle process and operation of the CureApp AUD App were evaluated, and the results demonstrated that the requirements were appropriately met. While a transitional period has been applied to the implementation of the provision of Article 12, paragraph 3, a comprehensive review was conducted taking into account the issues described later in Section "4.B Outline of the review conducted by PMDA." Based on the results, there are no problems with conformity to Article 12.

(4) PMDA's conclusion on the conformity of the CureApp AUD App to Article 17, which stipulates the general requirements for information provision to users through Information on Precautions, etc.:
As described later in Section "6.B Outline of the review conducted by PMDA," to ensure the efficacy and safety of the CureApp AUD App, it is important that users are fully informed on its correct usage so that the CureApp AUD App is used in accordance with the appropriate clinical positioning. PMDA therefore instructed the applicant to review the intended use of the CureApp AUD App and take necessary measures such as provision of Information on Precautions, etc.

PMDA comprehensively reviewed the conformity of the CureApp AUD App 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 for the CureApp AUD App as well as the system and status in accordance with JIS T 14971 "Medical devices—Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

The patient app runs on the patient's own mobile device and the doctor app runs on a web browser. PMDA asked the applicant to explain measures for cybersecurity assurance.

The applicant's explanation:
The applicant evaluated 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] were identified as cybersecurity risks. Risk control has been implemented by [redacted] to address these risks.

The above measures minimized cyber risks, and are considered acceptable. Because the CureApp AUD App runs on general-purpose mobile devices and terminals, the Information on Precautions, etc. section should provide the following cautionary advice: "Caution should be exercised to prevent malware infections and data breach in the use of the CureApp AUD App" and "Medical institutions must comply with the Security Guidelines for Medical Information Systems."

PMDA comprehensively reviewed the documents pertaining to risk management, taking into account the applicant's explanation about cybersecurity assurance and discussions 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 did not submit data on the process used to manufacture the CureApp AUD App, in accordance with the Notification titled "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 November 21, 2014).

5.B Outline of the review conducted by PMDA

PMDA concluded, in accordance with the above notification, that there was no particular problem with omitting the submission of data on the process used to manufacture the CureApp AUD App.

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

6.A Summary of the data submitted

The applicant submitted the results data from Study ALM-003, a clinical study conducted in Japan to evaluate efficacy and safety of the CureApp AUD App to support the clinical evaluation for this application (from February 6, 2023 to September 15, 2023).

6.A.(1) Study design

Study ALM-003 was a prospective, multicenter, parallel-group study conducted at 17 study centers in Japan to evaluate the efficacy and safety of the CureApp AUD App in patients with alcohol dependence whose goal was to reduce their alcohol consumption. Table 3 shows the outline of Study ALM-003.

Table 3. Outline of Study ALM-003

Item	Description
Objective	In this study, patients with alcohol dependence are divided into the intervention group in which subjects are to use the CureApp AUD App in addition to the psychosocial treatment in accordance with the procedure in the Treatment to Reduce Alcohol Consumption (pocket manual) and the control group in which subjects are, in addition to receiving guidance on alcohol consumption reduction, to use only the alcohol consumption record function of the CureApp AUD App from which the essential functions have been removed. The superiority in efficacy at Week 12 weeks (after enrollment*) and safety are evaluated between the groups.
Study design	Randomized, open-label, parallel-group, multicenter
Number of study centers	17 in Japan
Sample size	A total of 283 subjects; 140 subjects in the intervention group; 143 subjects in the control group
Key inclusion criteria	Patients with alcohol dependence who meet all the following criteria are eligible 1. Those aged ≥20 years at the time of obtaining written consent 2. Those diagnosed as alcohol dependent** as per the ICD-10 criteria 3. Those with a drinking risk level (DRL) of high or very high (average daily alcohol consumption of >60 g for males and >40 g for females) during the period from Week −4 to the day before Week 0 4. Those who can receive treatment on an outpatient basis 5. Those not having serious social or family problems caused by drinking alcohol 6. Those without serious organ dysfunction for which drinking alcohol may lead to life-threatening situations (e.g., malignancies, liver failure, moderate or more advanced cardiac failure [NYHA III or higher], or chronic kidney disease of eGFR <30 mL/min/1.73 m^2) 7. Those with a CIWA-Ar score of <10 points both at Week −4 and Week 0 8. Those who have been fully informed of the study after the provision of sufficient information, and have provided written informed consent confirming their willing to participate in the study 9. Those who use iPhone (iOS 14.0 or higher is installed) or Android smartphone (Android ver.10 or higher) on a daily basis
Key exclusion criteria	Patients who meet any of the following criteria are ineligible 1. Those with <6 heavy drinking days (HDDs) during the period from Week −4 to the day before Week 0 2. Those who have 5 consecutive days without drinking during the period from Week −4 to the day before Week 0

Item	Description
	3. Those who have dementia or intellectual disability 4. Those who participated in structured alcohol dependence treatment, or structured supporting program for alcohol consumption reduction, or self-help group within 4 weeks prior to Week −4 5. Those who have taken prohibited concomitant medication within 4 weeks prior to Week −4 6. Those who participated in a clinical study (intervention study) within 4 weeks prior to Week −4 7. Those who have participated in a preliminary clinical study of the previous version of the CureApp AUD App 8. Those determined to be at severe risk of suicide as determined by the investigator or subinvestigator, or those whose score of ≥1 on item 9 (item on suicidal ideation) of the Patient Health Questionnaire 9 at Week −4 9. Pregnant, lactating, or possibly pregnant women, or women who wish to become pregnant during participation in Study ALM-003 10. Those with no fixed address and phone number 11. Those considered ineligible by the investigator or subinvestigator
Primary endpoint	Change from baseline in HDDs at Week 12 HDDs are the number of drinking days over 4 weeks (days/28 days) on which pure alcohol consumption exceeded 60 g/day for men and >40 g/day for women. The pure alcohol consumption on each day is calculated at every visit based on the records on the subject's app using the Timeline Follow Back method.*** The number of HDDs is calculated using the following formula: [Total number of HDDs from the last visit to the day before this visit / (number of days from the last visit to the day before this visit − number of days with missing data)] × 28
Key secondary endpoints	1. Change from baseline in HDDs at Week 24 2. Change from baseline in total alcohol consumption (TAC) at Week 12 and Week 24 TAC is defined as the mean pure alcohol consumption per day (g/day) from the last visit to the day before this visit TAC is calculated using the following formula: Total pure alcohol consumption from the last visit to the day before this visit / (number of days from the last visit to the day before this visit − number of days with missing data) 3. Proportion of responders based on HDDs (at Week 12 and Week 24) The proportion of responders based on HDDs is defined as the proportion of subjects who had ≤4 HDDs/4 weeks at the timepoint. 4. Response low drinking risk level (RLDRL) (at Week 12 and Week 24) RLDRL is defined as the DRL at the timepoint being at or below "low." 5. Status of app use (intervention group only) 6. Change from baseline in each hematological examination parameter at Week 12 and Week 24
Safety endpoints	Adverse events and malfunction

* "Enrollment" in Study ALM-003 is defined as at "V2 (Week 0)" in Figure 3.

** A person is diagnosed as being alcohol dependent when ≥3 of the following 6 criteria continue concurrently ≥1 month or relapsed repeatedly in the past year: (1) strong desire: strong desire or sense of compulsion; (2) difficulties in controlling: difficulties in controlling alcohol drinking behavior (onset, termination, or level of use); (3) withdrawal symptoms: emergence of withdrawal symptoms due to quitting or cutting down alcohol consumption, drinking more alcohol to recover from or relieve withdrawal symptoms; (4) increase in tolerance: the amount of alcohol consumption increases to achieve the same intoxicating effects that were experienced before; (5) drinking becomes the center of life: important activities in life are given up because of alcohol, a great deal of time is spent in activities necessary to use or recover from the effects of alcohol; and (6) unable to stop harmful use: persisting with drinking alcohol despite clear evidence of harmful physical/mental consequences.

*** A method used to determine retrospective estimates of alcohol consumption based on days of week, holidays, personal days-off/events on calendar in a face-to-face interview between the interviewer and patient at a visit

In Study ALM-003, subjects were divided into the intervention group in which subjects were to use CureApp AUD App in addition to the psychosocial treatment in accordance with the procedure in the "Treatment to Reduce Alcohol Consumption, pocket manual, the first edition"[5] [in Japanese] (hereinafter referred to as Treatment to Reduce Alcohol Consumption [pocket

manual]) and the control group in which subjects were, in addition to receiving the psychosocial treatment in accordance with the above procedure, to use only the alcohol consumption record function of the CureApp AUD App. The superiority in efficacy at Week 12 (after enrollment) and safety were evaluated between the groups. After the screening period (28 ± 7 days), provided for eligibility assessment based on the amount of alcohol consumed and other data recorded by the alcohol consumption record function, eligible subjects were randomized to the intervention and control groups at a ratio of 1:1. At Week 12, subjects whose World Health Organization (WHO) drinking risk level (DRL)[ii] was classified as high or very high could use concomitant medications that help stop drinking or reduce alcohol consumption (Figure 3).

[ii] Drinking Risk Level: Drinking risk level classification based on health risks by WHO

	Amount of alcohol consumed (volume of alcoholic beverage [mL] × alcohol content [%] / 100 × 0.8 [specific gravity])	
	Male	Female
Very high	>100 g	>60 g
High	>60 g to ≤100g	>40 g to ≤60 g
Medium	>40 g to ≤60g	>20 g to ≤40 g
Low	≥1 g to ≤40g	≥1 g to ≤20 g

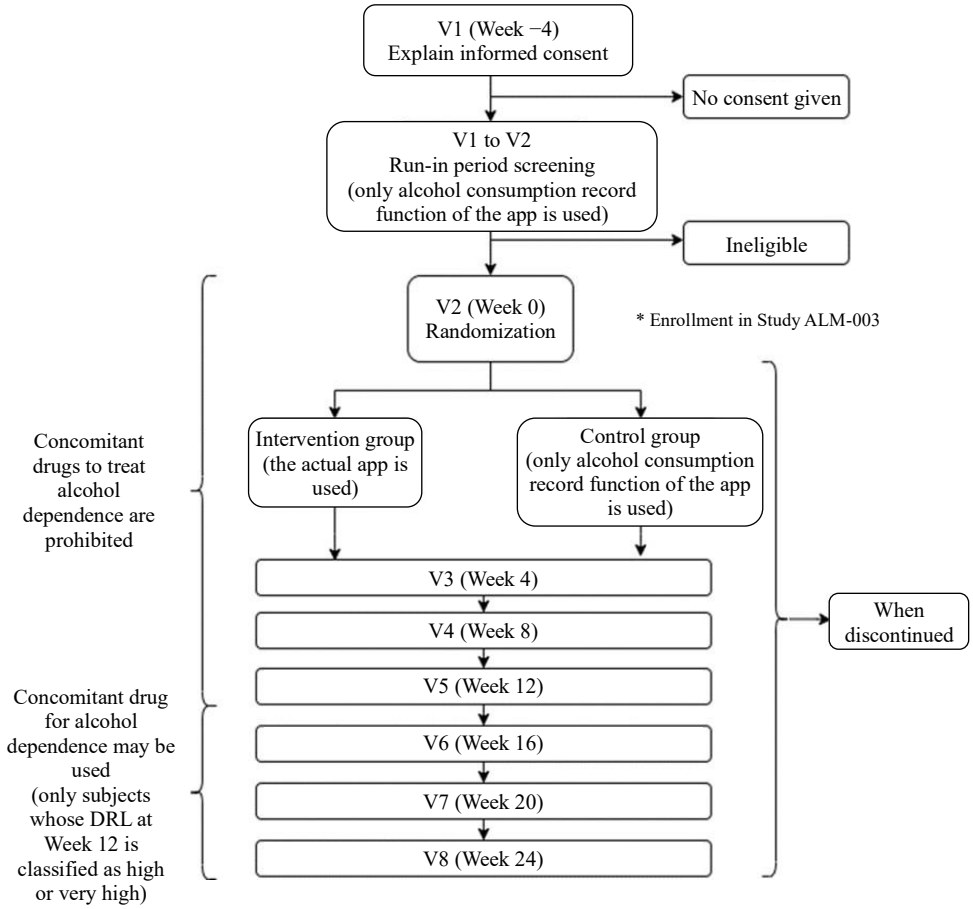


Figure 3. Outline of trial design

In Study ALM-003, change from baseline in HDDs at Week 12 was selected as the primary endpoint. It is known that there is a linear correlation between HDDs and mortality. The sample size was determined based on a report[6] that the hazard ratio of the mortality rate will decrease by 0.05 if HDDs per 4 weeks decrease by 2 days, as well as the literature[7,8] on change in HDDs for approved pharmaceutical products. At a 1:1 randomization ratio, assuming a between-group difference in the primary endpoint (change from baseline in HDDs at Week 12 between the intervention and control groups) of 2 days/4 weeks, and a standard deviation of 5.7 days/4 weeks, a sample size of 130 subjects would be required for each of the intervention and control groups to demonstrate significant difference at a two-sided significance level of 5% with 80% power. Therefore, a sample size of 260 subjects was selected. Figure 4 shows the patient disposition in Study ALM-003.

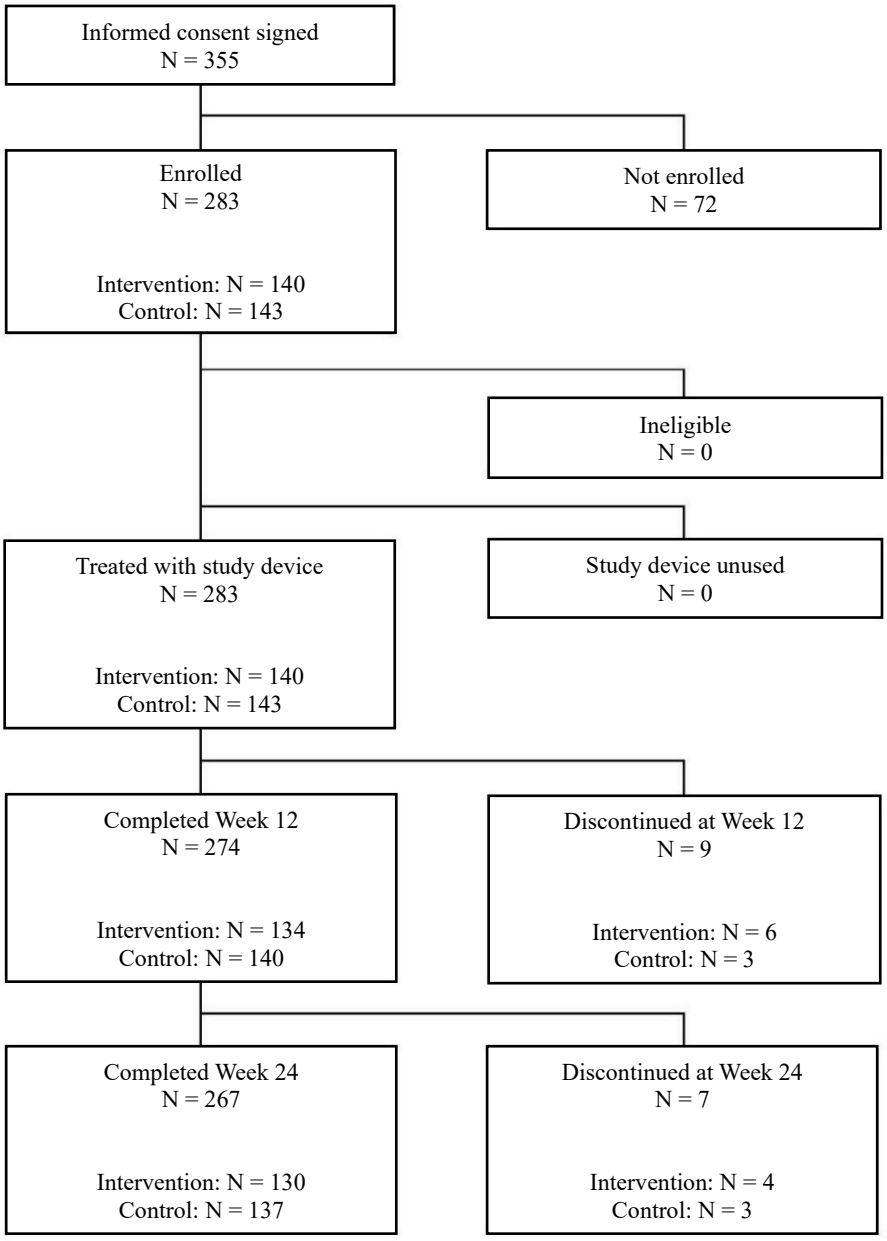


Figure 4. Patient disposition

From all subjects enrolled in Study ALM-003, subjects who did not meet the eligibility criteria and subjects who did not have post-randomization efficacy data were excluded, and the remaining subjects were included in the Full Analysis Set (FAS), which was the efficacy analysis population. Subjects with major protocol deviations that were considered to affect the efficacy evaluation were excluded from the FAS, and the remaining subjects were included in the Per Protocol Set (PPS). The Safety Analysis Set (SAF) comprised all enrolled subjects who received the study treatment at least once.

The SAF comprised all 283 subjects who enrolled in Study ALM-003 (140 subjects in the intervention group and 143 subjects in the control group) and the FAS comprised 278 subjects (136 subjects [97.1%] in the intervention group and 142 subjects [99.3%] in the control group). The PPS was the same as the FAS. Subjects who were enrolled in the study but excluded from the FAS were those who did not have post-randomization efficacy data. Figure 5 shows the patient disposition by analysis set.

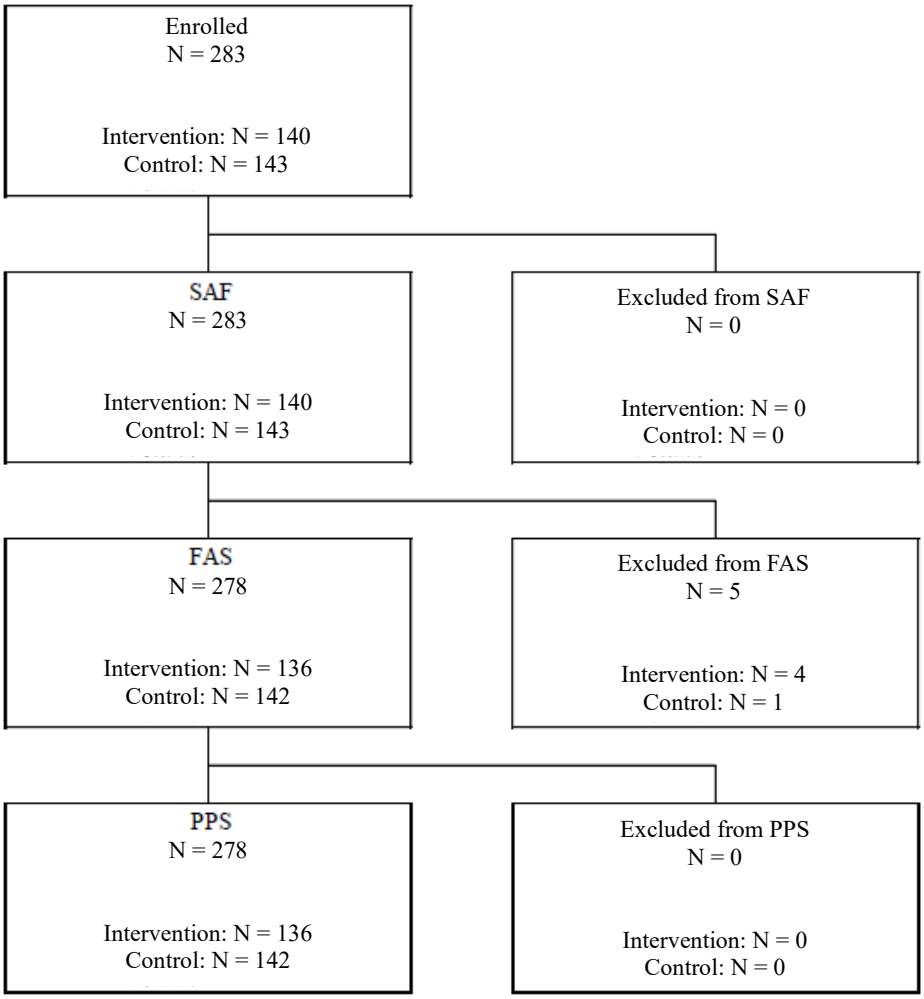


Figure 5. Patient disposition by analysis set

6.A.(2) Patient characteristics

Table 4 shows the characteristics of patients in the FAS in Study ALM-003.

Table 4. Patient characteristics of the FAS

Item	Category	Intervention	Control
Number of subjects	—	136	142
Age (years)	Mean	50.0	49.2
	Standard deviation	10.1	9.5
	Minimum	20	20
	Median	51.0	50.0
	Maximum	70	73
Sex	Male	90 (66.2)	88 (62.0)
	Female	46 (33.8)	54 (38.0)
Past or current smokers	Yes	82 (60.3)	82 (57.7)
	No	54 (39.7)	60 (42.3)
Current smokers	Yes	30 (22.1)	31 (21.8)
	No	52 (38.2)	51 (35.9)
Marital status	Married	94 (69.1)	101 (71.1)
	Unmarried	42 (30.9)	41 (28.9)
Employment status	Employed	119 (87.5)	120 (84.5)
	Unemployed	17 (12.5)	22 (15.5)
Age at first drink (years)	Mean	19.7	19.3
	Standard deviation	2.5	2.0
	Minimum	15	10
	Median	20.0	20.0
	Maximum	36	27
Age at which the subject noticed own drinking problem (years)	<40	62 (45.6)	63 (44.4)
	≥40 and <60	68 (50.0)	72 (50.7)
	≥60	6 (4.4)	7 (4.9)
Age at which drinking problem was pointed out by others (years)	<40	52 (38.2)	51 (35.9)
	≥40 and <60	72 (52.9)	80 (56.3)
	≥60	12 (8.8)	11 (7.7)
Prior treatment for alcohol dependence	Yes	1 (0.7)	2 (1.4)
	No	135 (99.3)	140 (98.6)
Family history of alcoholism	Yes	17 (12.5)	20 (14.1)
	No	119 (87.5)	122 (85.9)
Time since diagnosis of alcohol dependence to enrollment in Study ALM-003 (days)	Mean	25.3	40.1
	Standard deviation	4.0	178.4
	Minimum	21	21
	Median	26.0	27.5
	Maximum	43	2151
Drinking Risk Level (DRL)	Very high	62 (45.6)	64 (45.1)
	High	74 (54.4)	78 (54.9)

6.A.(3) Study results

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

Study ALM-003 was conducted to assess the superiority of the intervention over control in terms of reduction in HDDs. Change from baseline in HDDs at Week 12 was selected as the primary endpoint. Table 5 shows the summary statistics for HDDs at baseline and in the treatment period, and Table 6 shows the model analysis results for change from baseline in HDDs at Week 12.

Change from baseline in HDDs at Week 12 (adjusted mean ± standard error) was −12.237 ± 0.698 days/4 weeks in the intervention group and −9.453 ± 0.678 days/4 weeks in the control group. The difference in adjusted mean between the groups (lower bound to upper bound of the 95% CI) was −2.785 days/4 weeks (−4.666 days/4 weeks to −0.904 days/4 weeks), indicating that the intervention group showed a significant reduction compared to the control group (P = 0.0038).

Table 5. Summary statistics of HDDs at baseline and in the treatment period (days)

Timepoint	Treatment group	Number of subjects	Mean	Standard deviation	Min	Median	Max
Baseline	Intervention	136	23.151	4.928	8.00	24.091	28.00
	Control	142	23.133	4.713	10.00	24.367	28.00
Week 4	Intervention	134	15.509	8.915	0.00	15.691	28.00
	Control	140	18.206	7.892	0.00	18.667	28.00
Week 8	Intervention	135	12.490	9.882	0.00	10.667	28.00
	Control	139	15.674	8.844	0.00	16.000	28.00
Week 12	Intervention	133	10.478	9.424	0.00	8.615	28.00
	Control	138	13.457	8.646	0.00	12.800	28.00
Week 16	Intervention	130	9.867	9.368	0.00	7.252	28.00
	Control	135	12.293	8.744	0.00	10.000	28.00
Week 20	Intervention	132	9.207	9.051	0.00	6.500	28.00
	Control	134	11.339	8.852	0.00	10.250	28.00
Week 24	Intervention	128	8.638	9.112	0.00	5.125	28.00
	Control	136	10.360	8.694	0.00	9.000	28.00

Table 6. Model analysis results for change from baseline in HDDs at Week 12

		Baseline (N)	Week 12 (N)	Adjusted mean change	Difference between groups
HDDs (days/4 weeks)	Intervention	23.151 ± 4.928 (136)	10.478 ± 9.424 (133)	−12.237 ± 0.698	−2.785 (−4.666 to −0.904) P = 0.0038
	Control	23.133 ± 4.713 (142)	13.457 ± 8.646 (138)	−9.453 ± 0.678	

* An analysis was performed using mixed-effects models for repeated measures (MMRM) with timepoint, treatment, and timepoint-treatment interaction as fixed effects, individual subject as a random effect, and sex, age, and baseline HDDs as covariates.

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

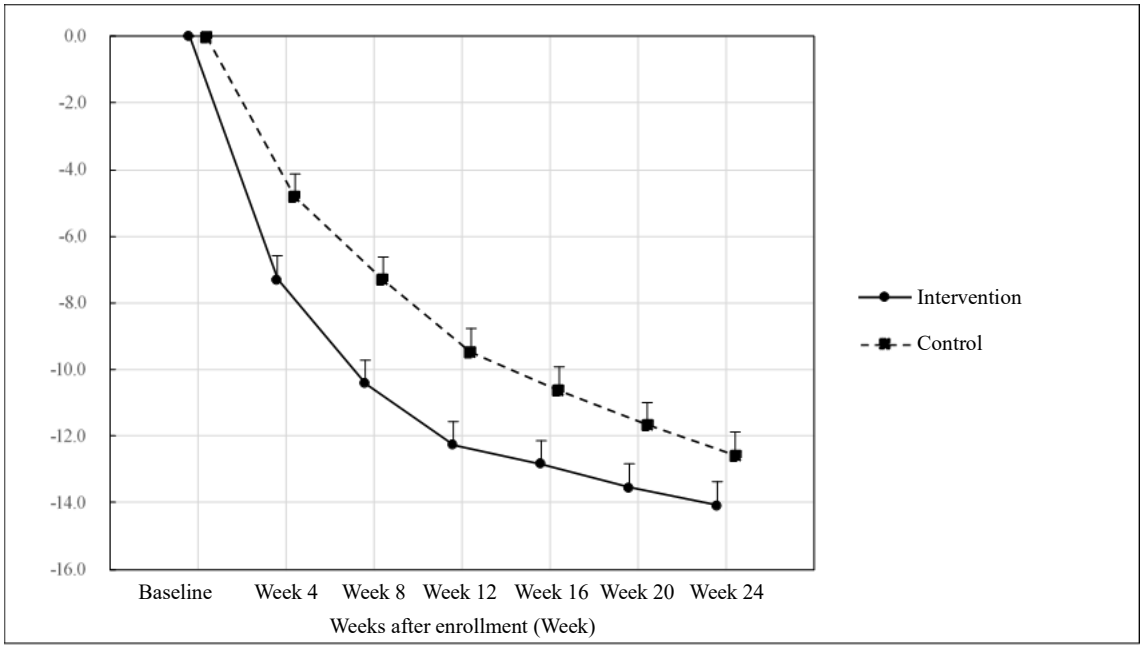
Results of key secondary endpoints are summarized below.

6.A.(3).2).(a) Change from baseline in HDDs at Week 24

Table 7. Change from baseline in HDDs at Week 24 (days/4 weeks)

Timepoint	Treatment group	Number of subjects	Change from baseline					
			Adjusted mean	Standard error	Difference in adjusted mean between groups	95% CI		*P*-value
						Lower	Upper	
Week 4	Intervention	134	−7.296	0.711	−2.486	−4.401	−0.570	0.0111
	Control	140	−4.811	0.690				
Week 8	Intervention	135	−10.422	0.710	−3.125	−5.039	−1.211	0.0014
	Control	139	−7.297	0.690				
Week 12	Intervention	133	−12.271	0.711	−2.806	−4.723	−0.888	0.0042
	Control	138	−9.465	0.691				
Week 16	Intervention	130	−12.853	0.714	−2.221	−4.146	−0.296	0.0238
	Control	135	−10.632	0.693				
Week 20	Intervention	132	−13.550	0.714	−1.872	−3.800	0.057	0.0571
	Control	134	−11.678	0.695				
Week 24	Intervention	128	−14.097	0.718	−1.506	−3.441	0.429	0.1269
	Control	136	−12.591	0.696				

* An analysis was performed using MMRM with timepoint, treatment, and timepoint-treatment interaction as fixed effects, individual subject as a random effect, and sex, age, and baseline HDDs as covariates.



* An analysis was performed using MMRM with timepoint, treatment, and timepoint-treatment interaction as fixed effects, individual subject as a random effect, and sex, age, and baseline HDDs as covariates.

Figure 6. Change from baseline in HDDs over time (adjusted mean + standard error)

6.A.(3).2).(b) Change from baseline in TAC at Week 12 and Week 24

Table 8. TAC at baseline and in the treatment period (g/day)

Timepoint	Treatment group	Number of subjects	Mean	Standard deviation	Min	Median	Max
Baseline	Intervention	136	88.250	30.285	40.69	82.475	222.25
	Control	142	87.908	33.684	41.05	81.555	298.79
Week 4	Intervention	134	60.150	28.092	0.50	54.720	184.31
	Control	140	69.751	29.066	28.48	65.105	199.70
Week 8	Intervention	135	53.537	26.977	0.00	47.160	160.59
	Control	139	62.281	27.981	16.80	56.070	198.23
Week 12	Intervention	133	48.422	28.471	0.00	42.530	158.56
	Control	138	54.262	25.604	12.74	51.135	164.42
Week 16	Intervention	130	45.735	27.964	0.00	40.475	163.57
	Control	135	50.051	23.291	0.00	46.080	144.37
Week 20	Intervention	132	43.164	27.101	0.00	38.850	147.89
	Control	134	47.974	24.871	8.97	43.290	149.26
Week 24	Intervention	128	41.892	28.423	0.00	37.760	164.96
	Control	136	44.799	23.890	4.35	41.805	145.60

Table 9. Change from baseline in TAC at Week 12 (g/day)

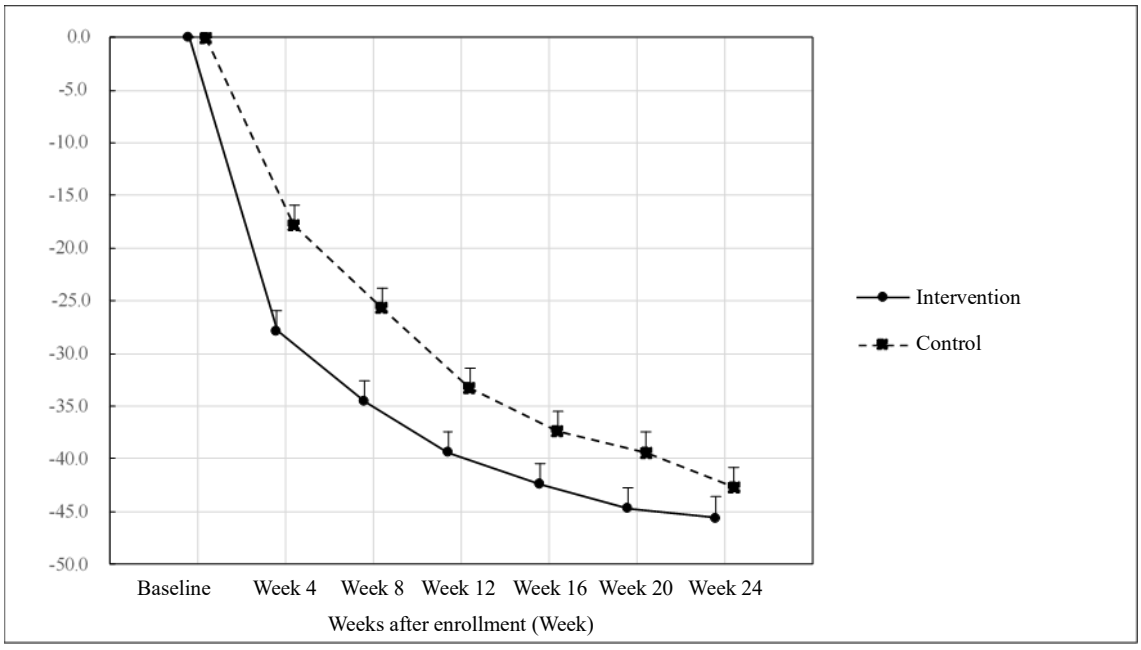
Timepoint	Treatment group	Number of subjects	Change from baseline					
			Adjusted mean	Standard error	Adjusted mean difference between groups	95% CI		*P*-value
						Lower	Upper	
Week 4	Intervention	134	−27.860	1.902	−10.033	−15.138	−4.928	0.0001
	Control	140	−17.827	1.845				
Week 8	Intervention	135	−34.555	1.899	−8.872	−13.972	−3.773	0.0007
	Control	139	−25.683	1.844				
Week 12	Intervention	133	−39.399	1.904	−6.095	−11.209	−0.982	0.0196
	Control	138	−33.304	1.848				

* An analysis was performed using MMRM with timepoint, treatment, and timepoint-treatment interaction as fixed effects, individual subject as a random effect, and sex, age, and baseline TAC as covariates.

Table 10. Change from baseline in TAC at Week 24 (g/day)

Timepoint	Treatment group	Number of subjects	Change from baseline					
			Adjusted mean	Standard error	Adjusted mean difference between groups	95% CI		*P*-value
						Lower	Upper	
Week 4	Intervention	134	−27.867	1.959	−10.046	−15.312	−4.780	0.0002
	Control	140	−17.821	1.902				
Week 8	Intervention	135	−34.565	1.956	−8.872	−14.134	−3.610	0.0010
	Control	139	−25.693	1.901				
Week 12	Intervention	133	−39.400	1.960	−6.119	−11.389	−0.849	0.0230
	Control	138	−33.281	1.903				
Week 16	Intervention	130	−42.369	1.966	−5.040	−10.327	0.247	0.0617
	Control	135	−37.329	1.909				
Week 20	Intervention	132	−44.658	1.968	−5.287	−10.583	0.009	0.0504
	Control	134	−39.371	1.913				
Week 24	Intervention	128	−45.596	1.978	−2.918	−8.232	2.396	0.2811
	Control	136	−42.678	1.916				

* An analysis was performed using MMRM with timepoint, treatment, and timepoint-treatment interaction as fixed effects, individual subject as a random effect, and sex, age, and baseline TAC as covariates.



* An analysis was performed using MMRM with timepoint, treatment, and timepoint-treatment interaction as fixed effects, individual subject as a random effect, and sex, age, and baseline TAC as covariates.

Figure 7. Change from baseline in TAC over time (adjusted mean + standard error)

6.A.(3).2).(c) Proportion of responders based on HDDs (at Week 12 and Week 24)

Responders were defined as subjects who had ≤4 HDDs/4 weeks. The efficacy data at Week 12 and Week 24 to derive the proportion of responders based on HDDs are shown in Table 11 and Table 12, respectively.

Table 11. Proportion of responders based on HDDs at Week 12

FAS with no missing value imputation

Treatment group	Number of subjects	Number of responders	Proportion of responders (%)	Cochran-Mantel-Haenszel test			
				Odds ratio	95% CI		*P*-value
					Lower bound	Upper bound	
Intervention	133	53	39.8	3.14	1.77	5.60	0.0001
Control	138	25	18.1				

* The Cochran-Mantel-Haenszel test adjusted for sex and baseline DRL was performed.

Table 12. Proportion of responders based on HDDs at Week 24

FAS with no missing value imputation

Treatment group	Number of subjects	Number of responders	Proportion of responders (%)	Cochran-Mantel-Haenszel test			
				Odds ratio	95% CI		*P*-value
					Lower bound	Upper bound	
Intervention	128	61	47.7	2.02	1.20	3.37	0.0069
Control	136	43	31.6				

* The Cochran-Mantel-Haenszel test adjusted for sex and baseline DRL was performed.

6.A.(3).2).(d) Response low drinking risk level (RLDRL) (at Week 12 and Week 24)

Subjects with RLDRL are defined as subjects with a DRL at or below "low." The efficacy data at Week 12 and Week 24 to derive the number of subjects with RLDRL and the proportion of subjects with RLDRL are shown in Table 13.

Table 13. Response low drinking risk level at Week 12 and Week 24

	Treatment group	Number of subjects	Number of subjects achieving RLDRL	Proportion of subjects achieving RLDRL (%)	Cochran-Mantel-Haenszel test			
					Odds ratio	95% CI		*P*-value
						Lower bound	Upper bound	
Week 12	Intervention	133	39	29.3	2.23	1.20	4.13	0.0099
	Control	138	22	15.9				
Week 24	Intervention	128	51	39.8	1.39	0.82	2.36	0.2197
	Control	136	44	32.4				

* The Cochran-Mantel-Haenszel test adjusted for sex and baseline DRL was performed.

6.A.(3).2).(e) Status of app use

Table 14 shows the summary statistics of app use status in the intervention group during the treatment period. The number of days the app was activated (mean ± standard deviation) (percentage of the days activated) was 21.677 ± 6.983 days/4 weeks (77.4%) at Week 12 and 19.841 ± 7.776 days/4 weeks (70.9%) at Week 24.

Table 14. Status of app use (intervention group only)

	Item*	Summary statistic					
		N	Mean	SD	Min	Median	Max
Week 4	Frequency of app activation (times)	134	155.836	93.500	17.00	142.667	455.00
	Number of days the app was activated (days)	134	24.462	4.985	5.00	27.000	28.00
	Drinking record entered within the same day (%)	134	69.7	30.4	3	82.0	100
	Drinking record entered by the next day (%)	134	91.2	17.0	17	100.0	100
	Frequency of entering [redacted] (times)	134	39.988	16.742	0.00	47.000	56.00
	Frequency of checking [redacted] (times)	134	28.209	31.376	0.00	19.500	161.00
	Frequency of implementing [redacted] (times)	134	10.886	13.964	0.00	5.000	85.00
	Frequency of implementing [redacted] (times)	134	1.954	4.428	0.00	0.000	35.00
Week 8	Frequency of app activation (times)	135	125.180	92.183	13.00	107.000	635.00
	Number of days the app was activated (days)	135	22.760	6.505	1.08	26.000	28.00
	Drinking record entered within the same day (%)	135	63.1	33.3	0	72.0	100
	Drinking record entered by the next day (%)	135	84.9	22.8	7	96.0	100
	Frequency of entering [redacted] (times)	135	37.844	19.064	0.00	48.125	56.00
	Frequency of checking [redacted] (times)	135	28.276	39.495	0.00	16.000	193.00
	Frequency of implementing [redacted] (times)	135	9.125	12.158	0.00	4.667	66.00
	Frequency of implementing [redacted] (times)	135	2.324	5.318	0.00	0.000	37.00
Week 12	Frequency of app activation (times)	133	114.405	107.299	4.00	88.000	971.00
	Number of days the app was activated (days)	133	21.677	6.983	1.33	24.267	28.00
	Drinking record entered within the same day (%)	133	59.8	34.5	0	67.0	100
	Drinking record entered by the next day (%)	133	82.7	23.8	4	96.0	100
	Frequency of entering [redacted] (times)	133	36.588	20.415	0.00	46.308	56.00
	Frequency of checking [redacted] (times)	133	29.258	42.085	0.00	11.200	221.33
	Frequency of implementing [redacted] (times)	133	8.353	11.466	0.00	4.000	60.15
	Frequency of implementing [redacted] (times)	133	2.363	5.065	0.00	0.000	30.07
Week 16	Frequency of app activation (times)	130	102.678	103.208	8.56	81.880	987.00
	Number of days the app was activated (days)	130	21.538	7.065	1.33	24.000	28.00
	Drinking record entered within the same day (%)	130	59.6	34.9	0	71.0	100
	Drinking record entered by the next day (%)	130	82.0	24.7	4	96.0	100
	Frequency of entering [redacted] (times)	130	36.230	21.155	0.00	46.684	56.00
	Frequency of checking [redacted] (times)	130	33.545	50.576	0.00	16.061	315.00
	Frequency of implementing [redacted] (times)	130	1.329	2.898	0.00	0.000	20.00
	Frequency of implementing [redacted] (times)	130	0.425	1.811	0.00	0.000	18.00
Week 20	Frequency of app activation (times)	132	95.700	95.570	6.40	77.300	953.00
	Number of days the app was activated (days)	132	21.017	7.005	3.00	23.346	28.00
	Drinking record entered within the same day (%)	132	57.8	34.4	0	63.0	100
	Drinking record entered by the next day (%)	132	81.2	25.8	7	95.0	100
	Frequency of entering [redacted] (times)	132	35.965	21.053	0.00	46.000	56.00
	Frequency of checking [redacted] (times)	132	34.072	51.960	0.00	15.500	316.00

	Item*	Summary statistic					
		N	Mean	SD	Min	Median	Max
	Frequency of implementing [redacted] (times)	132	1.085	3.174	0.00	0.000	15.00
	Frequency of implementing [redacted] (times)	132	0.412	1.812	0.00	0.000	13.00
Week 24	Frequency of app activation (times)	128	82.431	58.474	4.00	70.350	295.00
	Number of days the app was activated (days)	128	19.841	7.776	0.93	21.373	28.00
	Drinking record entered within the same day (%)	128	51.7	35.5	0	53.0	100
	Drinking record entered by the next day (%)	128	76.8	29.0	3	92.5	100
	Frequency of entering [redacted] (times)	128	33.423	21.972	0.00	43.038	56.00
	Frequency of checking [redacted] (times)	128	28.821	42.522	0.00	12.067	209.00
	Frequency of implementing [redacted] (times)	128	0.712	2.580	0.00	0.000	16.00
	Frequency of implementing [redacted] (times)	128	0.383	1.894	0.00	0.000	14.40

* With the exception of "drinking record entered within the same day (%)" and "drinking record entered by the next day (%)," the number of days or times per 28 days are calculated.

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

The SAF comprised 140 subjects in the intervention group and 143 subjects in the control group. Table 15 summarizes the adverse events that occurred after enrollment through study completion or discontinuation in Study ALM-003.

A total of 73 adverse events occurred in 46 of 140 subjects (32.9%) in the intervention group and 75 adverse events occurred in 48 of 143 subjects (33.6%) in the control group. Serious adverse events occurred in 2 of 140 subjects (1.4%) in the intervention group (pneumonia and tendon rupture [1 subject each, 0.7%]) and no serious events occurred in the control group. Adverse events leading to treatment discontinuation with the CureApp AUD App occurred in 1 of 140 subjects (0.7%) in the intervention group (worsening of preexisting condition [bipolar disorder]), with the outcome reported as unresolved at the time of discontinuation from the study, and 0 subjects in the control group. A causal relationship to the CureApp AUD App was ruled out for all adverse events.

Table 15. Summary of adverse events

	Intervention (N = 140)		Control (N = 143)	
	Number of events	Number of subjects with events (%)	Number of events	Number of subjects with events (%)
Adverse events	73	46 (32.9)	75	48 (33.6)
Serious adverse events	2	2 (1.4)	0	0 (0.0)
Adverse events leading to study device discontinuation	1	1 (0.7)	0	0 (0.0)

6.A.(3).4) Malfunctions

Table 16 summarizes malfunctions that occurred in Study ALM-003. A total of 26 malfunctions occurred in 24 of 140 subjects (17.1%) in the intervention group, while 4 malfunctions occurred in 4 of 143 subjects (2.8 %) in the control group. All the reported malfunctions were unexpected malfunctions. None of these malfunctions were likely to have an adverse effect on health. Table 17 shows the details of malfunctions.

Table 16. Summary of malfunctions occurring in Study ALM-003

	Intervention (N = 140)		Control (N = 143)	
	Number of events	Number of subjects with events (%)	Number of events	Number of subjects with events (%)
Malfunctions	26	24 (17.1)	4	4 (2.8)
Malfunctions that were likely to have a serious adverse effect on health	0	0 (0.0)	0	0 (0.0)
Unexpected malfunctions	26	24 (17.1)	4	4 (2.8)
Malfunctions that were likely to have an adverse effect on health	0	0 (0.0)	0	0 (0.0)

Table 17. Details of malfunctions

Malfunctions	Intervention (N = 140)		Control (N = 143)	
	Number of events	Number of subjects with events (%)	Number of events	Number of subjects with events (%)
Application program-related problems[*1]	9	9 (6.4)	4	4 (2.8)
Application program froze and stopped functioning[*2]	9	9 (6.4)	0	0 (0.0)
Program or algorithm execution-related problems[*3]	2	2 (1.4)	0	0 (0.0)
Computer operating system-related problems	2	2 (1.4)	0	0 (0.0)
Inappropriate or incorrect procedure or method	4	4 (2.9)	0	0 (0.0)
Total	26	24 (17.1)	4	4 (2.8)

*1. Problems such as malfunctioning during screen transition in the patient app, unsuccessful establishment of data linkage between the patient app and doctor app. These were dealt with by fixing the app (updating), re-entering data, etc.
*2. Malfunctions occurring in the doctor app, which were dealt with reloading the screen, etc.
*3. Encountering errors when entering data on the doctor app.

6.B Outline of the review conducted by PMDA

PMDA's review primarily focused on the following points:

(1) Study design of Study ALM-003

(2) The efficacy and safety of the CureApp AUD App

(3) Clinical positioning

6.B.(1) Study design of Study ALM-003

6.B.(1).1) Study population

PMDA'S view on the patient population of Study ALM-003:

The tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnostic criteria formulated by WHO have been used for the diagnosis of alcohol dependence and are provided in the Diagnostic and Treatment Guide and the Treatment to Reduce Alcohol Consumption (pocket manual). In the ICD-10 diagnostic criteria, a person is diagnosed as having alcohol dependence when ≥3 of the items in the criteria continue concurrently ≥1 month or there is repeated relapse in the preceding year. It also states that patients eligible for the treatment for alcohol consumption reduction should not meet any of the following criteria.

- Patients who require inpatient treatment
- Patients who have serious problems associated with drinking alcohol and difficulties in social and family lives
- Patients with serious organ impairment who are in an alcohol-associated life-threatening situation
- Patients with ongoing alcohol withdrawal symptoms that require immediate medical attention (e.g., hallucinations, seizures, delirium tremens)
- Patients who wish to completely abstain from alcohol

The eligible patients for Study ALM-003 were those with alcohol dependence according to the ICD-10 diagnostic criteria who did not meet any of the above-mentioned criteria, that is, patients for whom alcohol reduction treatment was a treatment option. Since the CureApp AUD App is to assist patients on alcohol reduction treatment, the population covered in Study ALM-003 is consistent with the population eligible for the CureApp AUD App. PMDA concluded that there were no particular problems in evaluating for the intended population based on the results from the Study ALM-003 population.

6.B.(1).2) Primary endpoint and evaluation period

The applicant's explanation about the primary endpoint and the evaluation period of the CureApp AUD App:

The number of HDDs has been shown to correlate with both short-term adverse consequences (e.g., stroke, accident, trauma) and long-term adverse consequences (e.g., death). It has been reported that the hazard ratio for mortality is reduced by 0.05 when the HDDs are reduced by 2 days per 4 weeks.[6] The change from baseline in HDDs at Week 12, the primary endpoint, is considered by European Medicines Agency (EMA) as an effective measure to assess the efficacy of treatment for alcohol dependence.[7,8] In addition, the CureApp AUD App is designed to

encourage patients to reduce heavy drinking by [redacted], and change in HDDs is an appropriate measure to evaluate the effectiveness of the CureApp AUD App.

The Treatment to Reduce Alcohol Consumption (pocket manual) recommends that the effectiveness of the treatment drugs in alcohol consumption reduction should be assessed every 3 months at a general healthcare institution: if the treatment is successful, similar treatment should be continued; if it is not successful, the patient should be referred to a specialized healthcare institution. Based on this, Week 12 was determined as a timepoint for the evaluation of the change from baseline in HDDs, the primary endpoint.

Taking into account comments from the Expert Discussion, PMDA concluded that the applicant's explanation was acceptable.

6.B.(2) The efficacy and safety of CureApp AUD App

6.B.(2).1) Efficacy

The applicant's explanation about the efficacy of the CureApp AUD App:

Change from baseline in HDDs at Week 12 (adjusted mean ± standard error) was −12.237 ± 0.698 days/4 weeks in the intervention group and −9.453 ± 0.678 days/4 weeks in the control group. The difference in adjusted mean between the groups was −2.785 days/4 weeks (95% CI: −4.666 days/4 weeks to −0.904 days/4 weeks). The intervention group showed a significant reduction compared to the control group (P = 0.0038), demonstrating the superiority of the CureApp AUD App over control. Change from baseline in TAC at Week 12 (adjusted mean ± standard error) was −39.399 ± 1.904 g/day in the intervention group and −33.304 ± 1.848 g/day in the control group. The difference in adjusted mean between the groups was −6.095 g/day (95% CI, −11.209 g/day to −0.982 g/day) (P = 0.0196), a result supporting the efficacy of the CureApp AUD App. There was a continuing reduction in the change from baseline to Week 24 both in HDDs and TAC. Change from baseline in HDDs at Week 24 was −14.097 ± 0.718 days/4 weeks, and change from baseline in TAC was −45.596 ± 1.978 g/day.

The Treatment to Reduce Alcohol Consumption (pocket manual) shows that the "Low" DRL (RLDRL in Study ALM-003) (mean alcohol consumption of ≤40 g/day for men and ≤20 g/day for women) is one of indications for treatment success. At Week 12, the proportion of subjects achieving RLDRL was 29.3% in the intervention group and 15.9% in the control group, with an odds ratio of 2.23 (95% CI, 1.20-4.13). The intervention group has significantly higher RLDRL compared to the control group (P = 0.0099). The proportion of subjects achieving RLDRL increased from 29.3% at Week 12 to 39.8% at Week 24.

The daily pure alcohol consumption in Study ALM-003 was based on the records entered on the app by the subject. In view of the accuracy in measuring the efficacy of the CureApp AUD App, PMDA asked the applicant to explain the appropriateness of the patient report-based evaluation, and consistency with other evaluations based on objective indicators.

The applicant's explanation:
The alcohol consumption used to calculate HDDs, the primary endpoint, was determined not based solely on the drinking record entered by the subject into the patient app. Instead it was amended using the Timeline Follow Back (TLFB) method, in which the subject reviews his/her past alcohol consumption in a face-to-face interview with the interviewer during a visit, referring to a calendar and considering days of week, holidays, personal days-off or events. The TLFB method is recommended in the EMA's Guideline for the development of medicinal products for the treatment of alcohol dependence. In Japan, the TLFB method is used as a primary endpoint for trials of drugs intended to reduce alcohol consumption, as well as in routine medical care, and is recognized as a reasonably reliable approach. It is a tool with a certain level of reliability. Before implementing TLFB, training sessions were held at the trial sites using educational materials including a manual to ensure the reliability of measured data.

One of the secondary endpoints, laboratory liver function test results, i.e., AST, ALT, and γ-GTP levels, showed that the values at Week 12 and Week 24 tended to be lower in the intervention group than in the control group (Table 18 through Table 23). Changes from baseline in these liver enzymes showed that worsening was prevented and liver functions tended to improve in the intervention group compared to the control group, supporting the efficacy of the CureApp AUD App as a therapeutic aid that helps reduce alcohol consumption.

Table 18. AST at baseline and in the treatment period (U/L)

Timepoint	Treatment group	Number of subjects	Mean	Standard deviation	Min	Median	Max
Baseline	Intervention	136	26.9	12.6	13	24.0	103
	Control	142	28.6	19.4	13	24.0	177
Week 12	Intervention	133	25.3	9.8	14	23.0	73
	Control	138	28.9	21.0	15	23.0	158
Week 24	Intervention	128	26.7	13.7	12	24.0	112
	Control	136	32.2	25.7	14	23.5	147

Table 19. Change from baseline in AST at Week 12 and Week 24

	Treatment group	Number of subjects	Generalized linear model						
			Least squares mean	Standard error	Estimated between-group difference	Standard error	95% CI		*P*-value
							Lower	Upper	
Change from baseline at Week 12	Intervention	133	−1.1	0.8	−1.9	1.2	−4.2	0.4	0.0971
	Control	138	0.8	0.8					
Change from baseline at Week 24	Intervention	128	0.2	1.4	−3.9	1.9	−7.6	−0.1	0.0441
	Control	136	4.0	1.3					

* Specifying treatment (intervention vs control) as a factor, sex, age, and each baseline hematological examination parameter as covariates

Table 20. ALT at baseline and in the treatment period (U/L)

Timepoint	Treatment group	Number of subjects	Mean	Standard deviation	Min	Median	Max
Baseline	Intervention	136	23.6	13.1	8	20.0	82
	Control	142	25.1	18.5	6	20.0	153
Week 12	Intervention	133	22.9	14.0	8	19.0	97
	Control	138	25.0	18.3	6	18.0	92
Week 24	Intervention	128	23.7	15.8	7	20.0	148
	Control	136	28.0	26.3	7	19.0	178

Table 21. Change from baseline in ALT at Week 12 and at Week 24

	Treatment group	Number of subjects	Generalized linear model						
			Least squares mean	Standard error	Estimated between-group difference	Standard error	95% CI		*P*-value
							Lower	Upper	
Change from baseline at Week 12	Intervention	133	−0.3	0.9	−0.9	1.3	−3.5	1.7	0.5037
	Control	138	0.5	0.9					
Change from baseline at Week 24	Intervention	128	0.4	1.4	−2.8	2.0	6.7	1.1	0.1646
	Control	136	3.2	1.4					

* Specifying treatment (intervention vs control) as a factor, sex, age, and each baseline hematological examination parameter as covariates

Table 22. Gamma-GTP at baseline and in the treatment period (U/L)

Timepoint	Treatment group	Number of subjects	Mean	Standard deviation	Min	Median	Max
Baseline	Intervention	136	73.6	85.1	12	44.0	464
	Control	142	75.3	88.7	12	42.0	499
Week 12	Intervention	133	63.5	97.7	11	40.0	792
	Control	138	74.1	109.1	10	38.0	717
Week 24	Intervention	128	65.5	86.5	11	44.5	662
	Control	136	76.8	113.8	11	40.0	799

Table 23. Change from baseline in γ-GTP at Week 12 and Week 24

	Treatment group	Number of subjects	Generalized linear model						*P*-value
			Least squares mean	Standard error	Estimated between-group difference	Standard error	95% CI		
							Lower	Upper	
Change from baseline at Week 12	Intervention	133	−4.7	4.6	−4.5	6.5	−17.3	8.4	0.4934
	Control	138	−0.2	4.6					
Change from baseline at Week 24	Intervention	128	−4.0	5.1	−5.4	7.2	−19.5	8.7	0.4546
	Control	136	1.4	5.0					

* Specifying treatment (intervention vs control) as a factor, sex, age, and each baseline hematological examination parameter as covariates

PMDA's view:

Study ALM-003 was an open-label study. Thus, the possibility cannot be ruled out that the obtained efficacy results was partly attributable to the Hawthorne effect, a phenomenon that occurs in a patient who is aware of being watched by someone such as a physician and alters behavior to meet their expectation, which consequently improved the symptoms. However, the goal management, self-monitoring, and result display functions contribute to the patient's [redacted]. Therefore, such effect is considered as a part of mechanism of how the CureApp AUD App exerts its efficacy. Given that the number of HDDs was calculated based on [redacted], the Hawthorne effect and the placebo effect should be taken into account in study planning as a general rule. In the control group, the subjects were provided with the app that only allowed the recording of alcohol intake and underwent self-monitoring, with an expectation of a certain degree of improvement. The intervention group demonstrated superiority to the conservative control group, and this indicates a significant improvement in the intervention group. Based on this outcome and discussions at the Expert Discussion, PMDA has concluded that it is acceptable to evaluate the efficacy of the CureApp AUD App based on the results of this open-label study.

Study ALM-003 also showed a significant reduction from baseline in HDDs at Week 12 in the intervention group compared to the control group. In addition, secondary endpoints of change from baseline in TAC at Week12, RLDRL, and liver function test improved in the intervention group compared to the control group consistently throughout the study.

Taking into account comments from the Expert Discussion, PMDA concluded that the efficacy of the CureApp AUD App has been demonstrated as an aid in psychosocial treatment for alcohol intake reduction.

6.B.(2).2) Safety

In the SAF (283 subjects total; 140 subjects in the intervention group and 143 subjects in the control group), the incidence of adverse events was 32.9% in the intervention group and 33.6% in the control group. Given that a causal relationship to the CureApp AUD App was ruled out for all adverse events, and that none of the malfunctions, which occurred in 17.1% of subjects, were likely to cause an adverse effect on health, PMDA concluded that there were no problems with the safety of the CureApp AUD App.

6.B.(2).3) Long-term efficacy and safety

The CureApp AUD App is designed to exert efficacy through repeated self-monitoring and goal management after the patient learns about psychosocial treatment for alcohol dependence up to [redacted]. In the post-marketing setting, the device is expected to be used continuously for a long time. PMDA asked the applicant to explain the long-term efficacy and safety of the CureApp AUD App.

The applicant's explanation:

After learning about the patient app content by [redacted], the patient continues with self-monitoring and personalized goal plan-based activities. Psychosocial treatment assisted by the CureApp AUD App aims to reduce alcohol intake based on the goal set, and exert its effect by encouraging [redacted]. Expected users will be alcohol dependent-patients whose likely treatment goal is to reduce alcohol intake. Physicians will ensure that patients fit this scope at every regular follow-up visit. The patient app will be locked after a long time absence from regular visits, and this implementation helps long-term use of the CureApp AUD App.

PMDA's view:

The differences in the change from Week 12 to Week 24 in HDDs and TAC between the intervention and control groups were smaller than those from baseline to Week 12, which suggests

a certain level of potential efficacy. However, a concern remains whether psychosocial treatment with the CureApp AUD App, in long-term use, continues to be highly effective compared to psychosocial treatment alone. Yet, the results are also indicative of the CureApp AUD App's contribution to early achievement of alcohol consumption reduction and its long-lasting effect. The Diagnostic and Treatment Guide describes psychosocial treatment as " a process of learning about dependence as a disease, understanding the purpose of treatment, and improving own attitudes toward alcohol and drinking habits at their own pace, with support from healthcare professionals. Psychosocial treatment plays a key role in continuous treatment for alcohol dependence." This emphasizes the importance of continuity of treatment. With the CureApp AUD App, patients will complete the learning about psychosocial treatment for alcohol dependence by [redacted]. After [redacted] of treatment period, it is important for patients to keep the low dinking level achieved by [redacted] of treatment period based on the knowledge and attitudes learned, and strive for further improvement. The self-monitoring and goal management functions of the CureApp AUD App are also available after [redacted] of treatment period to assist in continuous psychosocial treatment by healthcare professionals, and these functions should be available even after Week 24. Based on the fact that there were no safety-related problems up to Week 24, and in view of the discussions at the Expert Discussion, PMDA has concluded that there is no need to limit the duration of treatment with CureApp AUD App.

6.B.(3) Clinical positioning

6.B.(3).1) Intended use or indication

PMDA's view:

The intervention group in Study ALM-003 used the CureApp AUD App in addition to psychosocial treatment in accordance with the procedure specified in the Treatment to Reduce Alcohol Consumption (pocket manual). The efficacy and safety of the CureApp AUD App were demonstrated in patients in the intervention group. In light of the discussions at the Expert Discussion, the CureApp AUD App should be recognized as a medical device that assists in psychosocial treatment, and the CureApp AUD App should be approved with the following intended use or indication.

Intended Use or Indication

Aid in the treatment for alcohol consumption reduction in patients with alcohol dependence

6.B.(3).2) Healthcare institutions and providers using the CureApp AUD App

The applicant's explanation about the healthcare institutions and persons using the CureApp AUD App:

One of the development concepts of the CureApp AUD App was to provide treatment for alcohol dependence not only by specialized healthcare institutions but also by a wide range of healthcare providers. In line with the concept, in Study ALM-003, there were no restrictions regarding the department, board-certified physician qualification or board-certified specialist qualification of the investigators and subinvestigators of the study; however, they were required to receive the training programs. There were 2 training programs below, and the completion of both programs was mandatory.

- "E-learning training on the diagnosis and treatment of alcoholism"[iii] or "training course for clinicians providing alcohol dependence treatment" organized by the Kurihama Medical and Addiction Center
- A CureApp AUD App proper use training program by the CureApp, Inc. jointly developed with internal medicine specialists and psychiatrists specialized in alcohol dependence

The provision of similar types of training programs on the treatment of alcohol dependence or medical care with aiding apps will give healthcare providers, including non-specialized healthcare institutions and physicians, opportunities to use the CureApp AUD App in the post-marketing settings.

PMDA's view:
In Study ALM-003, the efficacy and safety of the CureApp AUD App were demonstrated under the conditions expected for the CureApp AUD App regardless of whether it was used by specialized healthcare institutions/specialists or non-specialized healthcare providers. Based on the discussions at the Expert Discussion, there are no problems with the applicant's plan. In the "New Diagnostic and Treatment Guidelines for Alcohol and Drug use Disorders," Diagnostic and Treatment Guide, and Treatment to Reduce Alcohol Consumption (pocket manual), it is assumed that treatment for alcohol consumption reduction may be provided by non-specialized healthcare providers. These guidelines also show how to deal with issues that may arise during treatment and when patients should be referred to specialized healthcare institutions, emphasizing the importance of working in collaboration with such institutions. Thus, when the CureApp AUD App is used to reduce alcohol consumption, the applicant should ensure that cautionary statements are included in the Information on Precautions, etc. alerting all healthcare providers using the app to work in collaboration with specialized healthcare institutions as necessary to avoid losing opportunities for patients to receive specialized care.

[iii] Hosted by the Japanese Medical Society of Alcohol and Addiction Studies and the Japan Society of Hepatology.

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 safety of the CureApp AUD App was evaluated in the clinical trial conducted under conditions similar to the use expected in post-marketing settings. There were no events suggestive of device-associated safety issues, and no particular concerns were identified. Accordingly, the applicant did not submit post-marketing surveillance plan because the CureApp AUD App was not designated for a use-results survey.

7.B Outline of the review conducted by PMDA

PMDA considers that safety concerns resulting from the CureApp AUD App in post-marketing settings are minimal because (1) the clinical trial involved patients and physicians for whom the CureApp AUD App is intended, and there were no adverse events for which a causal relationship to the CureApp AUD App could not be ruled out; (2) if a patient has not received medical advice and guidance from the physician for an extended period of time, the patient app will be locked and its use will be suspended; and (3) the CureApp AUD App is only used under the guidance of physicians. Based on the above as well as the discussions at the Expert Discussion, PMDA concluded that the CureApp AUD App did not need to be designated as a medical device subject to a use-results survey because there was no issue to be newly assessed.

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 CureApp AUD App is intended for patients with alcohol dependence for whom alcohol reduction treatment is indicated. The key issues in the review are (1) the efficacy and safety, and (2) the clinical positioning of the CureApp AUD App. The following describes PMDA's conclusions based on the discussions at the Expert Discussion.

(1) The efficacy and safety of the CureApp AUD App

In Study ALM-003, the CureApp AUD App was used as an aid for patients for whom alcohol reduction treatment was indicated and demonstrated its efficacy in the reduction of alcohol consumption. PMDA has concluded that there are no particular safety concerns, in view of no adverse events for which a causal relationship to the CureApp AUD App could not be ruled out or no malfunctions likely to harm health revealed in the study.

The self-monitoring and goal management functions of the CureApp AUD App assist in continual psychosocial treatment. These functions, which are essential for continuous treatment for alcohol consumption reduction, raised no particular safety-related concerns in Study ALM-003. Therefore, there is no need to limit the treatment duration with the CureApp AUD App.

(2) Clinical positioning

Study ALM-003 demonstrated a certain level of efficacy and safety of the CureApp AUD App as an aid in psychosocial treatment according to the procedure as per the Treatment to Reduce Alcohol Consumption (pocket manual) for patients with alcohol dependence for whom alcohol reduction treatment is indicated. Therefore, the CureApp AUD App should be recognized as a medical device that assists in psychosocial treatment.

Based on the above, PMDA has concluded that the CureApp AUD App may be approved for the intended use shown below.

Intended Use

Aid in the treatment for alcohol consumption reduction in patients with alcohol dependence

The product is not classified as a biological product or a specified biological product. The product does not need the designation as a medical device subject to a use-results survey.

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

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