March 9, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Program 2, Software for treatment of diseases
Term Name	Supporting software for hypertension treatment (newly created)
Brand Name	CureApp HT Digital Therapeutic App for Hypertension Treatment
Applicant	CureApp, Inc.
Date of Application	May 25, 2021 (Application for marketing approval)

Results of Deliberation

In its meeting held on March 9, 2022, the Subcommittee on Software as a Medical Device of the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product should be approved 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.

The product should be approved with the following condition.

Approval Condition

The applicant is required to collect post-marketing information on the efficacy of the product annually after approval and to report it to the Pharmaceuticals and Medical Devices Agency to verify that the efficacy of the product is maintained.

The brand name of the product should be “CureApp HT Digital Therapeutic App for Hypertension Adjunctive Treatment.”

Review Report

February 15, 2022
Pharmaceuticals and Medical Devices Agency

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

Classification	Program 2, Software for treatment of diseases
Term Name	Supporting software for hypertension treatment (to be newly created)
Brand Name	CureApp HT Digital Therapeutic App for Hypertension Adjunctive Treatment*
Applicant	CureApp, Inc.
Date of Application	May 25, 2021
Reviewing Office	Office of Software as a Medical Device

* The brand name of the product was modified based on the deliberation in the meeting of the Subcommittee on Software as a Medical Device of the Committee on Medical Devices and *In-vitro* Diagnostics held on March 9, 2022.

Review Results

February 15, 2022

Classification	Program 2, Software for treatment of diseases
Term Name	Supporting software for hypertension treatment (to be newly created)
Brand Name	CureApp HT Digital Therapeutic App for Hypertension Adjunctive Treatment*
Applicant	CureApp, Inc.
Date of Application	May 25, 2021

Results of Review

"CureApp HT Digital Therapeutic App for Hypertension Adjunctive Treatment*" (hereinafter referred to as CureApp HT App) is a digital therapeutic software program for patients with essential hypertension. CureApp HT App consists of a software application for patients that is installed on a smartphone or other mobile device before use ("patient app") and a software application for physicians ("physician app"). It is used in combination with the standard therapy for hypertension. CureApp HT App provides a platform where physicians and patients share blood pressure goals. CureApp HT App is intended to encourage patients to make behavioral changes in accordance with the treatment guidance that is tailored to each individual patient, so that lifestyle modifications will enhance the antihypertensive effect of standard therapy.

The applicant submitted non-clinical data supporting the software development life cycle process and performance of CureApp HT App. There was no particular problem in the submitted data.

The applicant submitted clinical data from a prospective, multicenter, parallel-group, controlled-study (the HERB trial) that evaluated the efficacy and safety of CureApp HT App. The HERB trial was conducted to evaluate the efficacy and safety of CureApp HT App in patients with Grade I or II essential hypertension who were aged ≥20 and <65 years, had received no antihypertensive medication, and were expected to be able to manage their hypertension by modifying lifestyle habits, such as diet and exercise.

The primary endpoint of the trial was the "change in mean 24-hour ambulatory systolic blood pressure from baseline to Week 12." A between-group comparison of the primary endpoint by analysis of covariance revealed that the least squares mean ± standard error was −4.9 ± 1.23 mmHg in the intervention group and −2.5 ± 1.30 mmHg in the control group, with an estimate of the between-group difference in the change (change in the intervention group − change in the control group) of −2.4 mmHg (95% confidence interval [CI], −4.5 to −0.3 mmHg). The change in the intervention group

* The brand name of the product was modified based on the deliberation in the meeting of the Subcommittee on Software as a Medical Device of the Committee on Medical Devices and *In-vitro* Diagnostics held on March 9, 2022.

was significantly greater than that in the control group. The trial also showed that the proportion of patients who successfully managed hypertension tended to be higher in the intervention group than in the control group. These results suggest that CureApp HT App is expected to help patients make and maintain lifestyle modifications. The effect of CureApp HT App is [redacted]. The patient app is locked if the patient does not receive a medical consultation from their treating physician for an extended period of time. CureApp HT App is intended to be used as an aid to help patients modify their lifestyle habits under the supervision of their treating physicians. For these reasons, CureApp HT App is unlikely to pose any particular risk to patients. On the basis of these clinically significant therapeutic results shown in the trial, PMDA concluded that the clinical efficacy of CureApp HT App outweighed its risk.

Among the target patient populations for CureApp HT App to be enrolled in the clinical trial originally designed by the applicant, patients with Grade III hypertension, elderly patients, and pediatric patients were not included in the HERB trial. Patients with Grade III hypertension and elderly patients receive advice on lifestyle modifications in addition to the standard treatment, as with the patient population of the HERB trial. The use of CureApp HT App is expected to enhance the antihypertensive effect of the standard treatment by aiding physicians in giving guidance on lifestyle modifications. However, strenuous exercise, or a delay in or deviation from standard treatment may pose a health risk to patients with Grade III hypertension. The above risks will be clinically acceptable because the following measures are taken: (1) [redacted], and (2) users are informed of precautions about these related risks by publishing information on precautions, etc. or providing such information in the instructions for use and other documents ("Information on Precautions, etc."). Elderly patients may be unable to use CureApp HT App properly because of their impaired cognitive function. A warning about this risk should be included in the Information on Precautions, etc. The efficacy of CureApp HT App in pediatric patients remains unknown because (i) the diagnostic criteria and treatment policy for hypertension differ between pediatric patients and adult patients, and (ii) CureApp HT App is not designed to be used in pediatric patients. Based on the above, patients with Grade III hypertension and elderly patients can be included in the target patient populations of CureApp HT App, but pediatric patients should not.

The patient app of CureApp HT App provides patients with knowledge about hypertension treatment. This app is also intended to encourage patients to make lifestyle modifications that may contribute to lowering blood pressure and to keep these new habits. Such characteristics of CureApp HT App preclude identifying factors influencing users' behavioral change. The magnitude of the impact of a change in message content on the efficacy and safety of the treatment cannot be assessed without clinical evaluation. In addition, when content presented by CureApp HT App becomes outdated as time goes by or people's lifestyle changes because of external factors, such as a pandemic of an infectious disease, guidance by the patient app may not lead to a similar behavior change to that achieved in the clinical trial, possibly resulting in the reduced efficacy of CureApp HT App. In order to maintain the efficacy of CureApp HT App, therefore, it is critical to update message content, interface, and other features of the patient app in a timely manner so that they match the times and lifestyle. Considering the indication, clinical positioning, mechanism of action, and limited use (only under the supervision of physicians) of CureApp HT App, the risk of CureApp HT App for patients is

negligible. Based on the above, in order to maintain the clinical efficacy of CureApp HT App, it is critical to update the interface and other features of the patient app and ensure that such improvements do not result in a substantial impairment of the efficacy of CureApp HT App.

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

Intended Use

Adjunctive treatment of essential hypertension in adults

Approval Condition

The applicant is required to collect post-marketing information on the efficacy of the product annually after approval and to report it to the Pharmaceuticals and Medical Devices Agency to verify that the efficacy of the product is maintained.

Review Report

February 15, 2022

Product for Review

Classification	Program 2, Software for treatment of diseases
Term Name	Supporting software for hypertension treatment (to be newly created)
Brand Name	CureApp HT Digital Therapeutic App for Hypertension Adjunctive Treatment*
Applicant	CureApp, Inc.
Date of Application	May 25, 2021
Proposed Intended Use	Treatment of essential hypertension

Table of Contents

* The brand name of the product was modified based on the deliberation in the meeting of the Subcommittee on Software as a Medical Device of the Committee on Medical Devices and *In-vitro* Diagnostics held on March 9, 2022.

List of Abbreviations

ABPM	Ambulatory blood pressure monitoring
BMI	Body mass index
DBP	Diastolic blood pressure
FAS	Full analysis set
SBP	Systolic blood pressure

I. Product Overview

"CureApp HT Digital Therapeutic App for Hypertension Adjunctive Treatment∗" (hereinafter referred to as CureApp HT App) is a digital therapeutic software program for patients with essential hypertension. CureApp HT App consists of a software application for patients that is installed on a patient's smartphone or other general-purpose mobile device before use ("patient app") and a software application for physicians that allows physicians to view data recorded on the patient app during a medical consultation (" physician app"). CureApp HT App provides a platform where physicians and patients share blood pressure goals. CureApp HT App encourages patients to make behavioral changes in accordance with the treatment guidance that is tailored to each individual patient, thus helping the patients modify their lifestyle habits for the management of hypertension. CureApp HT App is intended to be used under the supervision of physicians. The use of the patient app will be suspended if the patient does not receive a medical consultation from their treating physician for an extended period of time.

The Guidelines for the Management of Hypertension 2019[1] ("Guidelines for the Management of Hypertension") recommend lifestyle modifications as a useful option for not only patients receiving non-pharmacological therapy but also patients receiving pharmacological therapy. However, in most cases, patients can only receive guidance from their treating physicians during a short outpatient visit. It is physically impossible for physicians to provide patients with real-time advice in daily living outside of outpatient hours or long-term guidance. CureApp HT App is intended to provide patients with lifestyle guidance not only on an outpatient basis but also on a daily basis through the patient app to encourage patients to modify their lifestyle habits more effectively than conventional approaches.

An overview of the functions of the patient app and the physician app is presented below.

The content of the patient app is mainly based on the Guidelines for the Management of Hypertension. CureApp HT App tells patients about what they need to do to modify their lifestyle habits for the management of their hypertension by providing knowledge and recommended lifestyle behaviors based on the personality, environment, and other conditions of each individual patient, as well as presenting information and messages that encourage patients to make these lifestyle behaviors into a habit. Table 1 shows the major functions of the patient app.

Table 1. Overview of the functions of the patient app

Function	Description
Patient education	[redacted]
Action planning and implementation	[redacted]
Building new habits	[redacted]
Motivation	[redacted]

∗ The brand name of the product was modified based on the deliberation in the meeting of the Subcommittee on Software as a Medical Device of the Committee on Medical Devices and *In-vitro* Diagnostics held on March 9, 2022.

[redacted]

The treatment scheme of the patient app consists of the following 3 steps.

Step 1 is a step to acquire knowledge. First, patients enter information about their work situation and preference. The software of the app analyzes the data entered by patients to determine their characteristics, based on which, content is adjusted for the following aspects in the context of hypertension management: (1) reduction in salt intake, (2) weight loss, (3) exercise, (4) alcohol reduction, (5) sleep condition, (6) stress management, (7) smoking cessation, (8) disease understanding, and (9) blood pressure measurement. Then, the resulting content is presented on the app screen. Further, some details of the content displayed for the above 9 items will be adjusted based on information entered by patients, such as renal condition, usual exercise, and drinking habits. Once Step 1 is completed, the app navigates patients to Step 2.

Step 2 is to plan and implement healthy lifestyle behaviors. The software tailors and presents behavioral goals regarding salt reduction, weight loss, exercise, alcohol reduction, sleep condition, stress management, and smoking cessation. Patients check their behavioral goals and enter the results of their lifestyle behaviors into the app. Some behavioral goals in this step are also adjusted in accordance with information entered by patients. Once Step 2 is completed, the app navigates patients to Step 3.

Step 3 is to make healthy lifestyle behaviors a habit. Patients themselves decides blood pressure goals and enter their blood pressure measurements into the app. The patient app preferentially presents lifestyle behaviors recognized as highly effective by patients themselves in Step 2 to encourage patients to turn those lifestyle modifications into a habit.

Each step offers some functions to encourage the use of the patient app. For example, the app displays where the patient is currently in the treatment process. In addition, there are functions that motivate patients to enter measurements of salt intake.

The physician app helps physicians guide their patients by allowing healthcare professionals to access patient's information entered on the patient app through the Internet so that healthcare professionals know patient's blood pressure and lifestyle behaviors outside of medical consultations. With this app, physicians can check patient's information, clinical course, and the progress of use of the patient app.

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

The data submitted in the present application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

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

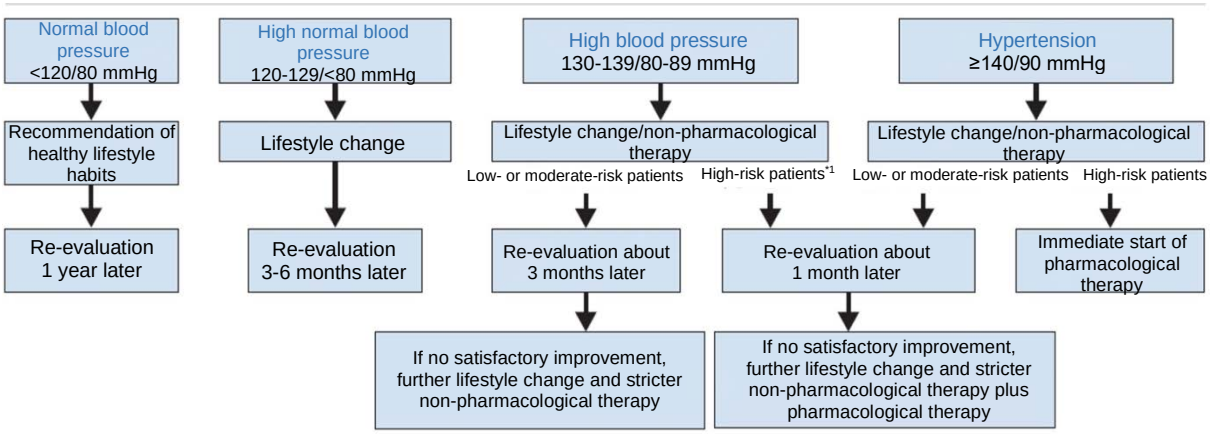
1. Origin or History of Development, Use in Foreign Countries, and Other Information

1.(1) History of development

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

Essential hypertension is treated with non-pharmacological therapy, including lifestyle modifications, and pharmacological therapy. Changing lifestyle habits is important for patients who have not yet started pharmacological therapy because lifestyle modification alone can reduce blood pressure. In contrast, lifestyle modification is also beneficial for patients who are on pharmacological therapy because it can enhance the effect of an antihypertensive drug (Figure 1). However, many patients are likely to fail to achieve preset blood pressure goals through lifestyle modification alone. This is a challenge of this approach.

To change lifestyle habits, patients are given advice on their diet, including a reduction in salt intake to <6 g per day and low animal fat intake, routine exercise (aerobic exercise), smoking cessation, weight control, etc. Patients with mild hypertension may be able to achieve normal blood pressure by modifying their lifestyle habits. If diet and exercise alone fail to improve the condition, the use of an antihypertensive drug is required.



*1 High-risk patients with high blood pressure levels include those aged ≥75 years and those with bilateral carotid stenoses or major cerebral artery occlusion. Patients with high blood pressure levels who have unevaluated cerebrovascular disorder, CKD without proteinuria, or non-valvular atrial fibrillation should be treated as moderate-risk patients even if they are classified as high-risk patients. The use of pharmacological therapy is considered on an individual patient basis in the course of lifestyle change and non-pharmacological therapy.

Figure 1. Hypertension management plan by blood pressure level at initial consultation (Source: the Guidelines for the Management of Hypertension)

A research paper has reported that dietary interventions involving dieticians, such as salt intake reduction, in addition to conventional advice given by a physician at outpatient visits, resulted in further reductions in blood pressure and salt intake.[2] There is room for improvement in the current lifestyle guidance given within limited outpatient service hours. Another research paper revealed that patients with hypertension are very conscious about salt reduction, but do not necessarily put it into practice.[3] It is important to give patients advice on lifestyle modification so that they can actually put the advice into practice and keep track of their salt intake for assessment. Continuing lifestyle modifications, including salt intake reduction, for a long period of time is not easy.[4] To help patients keep lifestyle changes, appropriate intervention is required. In clinical practice, however, giving real-time therapeutic intervention that encourages patients to make healthy lifestyle behaviors is physically difficult outside of outpatient consultations. For these reasons, the Japanese Guidelines for the Management of Hypertension and the US guidelines for hypertension management (2017)[5]

describe expectations for the development of an effective intervention using information and communication technology.[6]

CureApp HT App was developed to encourage patients to change lifestyle habits more effectively than conventional approaches by providing patients with information regarding lifestyle modifications that is available outside of outpatient consultations on behalf of physicians and by collecting and sharing patients' data outside of outpatient consultation hours.

1.(2) Use in foreign countries

CureApp HT App is not approved or licensed in foreign countries.

2. Specifications

2.(1) Performance and safety specifications

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

The proposed performance specifications for CureApp HT App include the functions of the patient app (for patient education, action planning and implementation, building new habits, and motivation) and those of the physician app (for a series of operations, including the presentation of information that is used by physicians as an aid to guide patients). The proposed safety specification for CureApp HT App is the 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 was no particular problem with the specifications.

2.(2) Safety specifications

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

The applicant submitted the data indicating a summary of each stage of the life cycle process required for safety design and maintenance of CureApp HT App in accordance with JIS T 2304: 2017 "Medical device software - Software life cycle processes."

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

PMDA comprehensively reviewed the data regarding the software life cycle process, taking into consideration the later discussion in Section "3.B Outline of the review conducted by PMDA," and concluded that there was no particular problem.

2.(3) Performance

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

The applicant submitted the data supporting the performance of the patient app and the physician app, i.e., data regarding the evaluation of appropriate performance of each function.

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

PMDA reviewed the data regarding the evaluation of appropriate performance of each function and concluded that there was no particular problem with these functions.

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

3.B Outline of the review conducted by PMDA

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

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

PMDA's view:

As described later in Section "6.B Outline of the review conducted by PMDA," to ensure the efficacy and safety of CureApp HT App, users should be fully informed of treatment with CureApp HT App before starting the therapy so that CureApp HT App is used in accordance with its clinical positioning. For this reason, PMDA instructed the applicant to re-consider the intended use of CureApp HT App and take necessary measures, such as publishing information on precautions, etc. or providing such information in the instructions for use and other documents ("Information on Precautions, etc.").

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

PMDA's view:

As described later in Section "6.B Outline of the review conducted by PMDA," the clinical trial demonstrated a certain level of clinically significant antihypertensive effect of CureApp HT App. There was no problem with the conformity of CureApp HT App to Articles 3 and 6.

(c) The conformity of CureApp HT App to Article 9, paragraph (6), which stipulates the environment in which medical devices are intended to be used

PMDA's view (based on the characteristics of CureApp HT App):

The patient app of CureApp HT App provides patients with knowledge about hypertension treatment. The patient app is also intended to encourage patients to make lifestyle modifications that may contribute to lowering blood pressure and to keep these new habits. How the patient app display messages, etc. and how the interface, etc. of the app work (hereinafter collectively referred to as "the output specifications") can have a direct impact on the patient's learning progress and motivation to

start and continue new lifestyle behaviors. Because of these characteristics of CureApp HT App, whether a change in the output specifications affects the efficacy of the therapy cannot be assessed without clinical evaluation.

In addition, when the output specifications become outdated as time goes by or people's lifestyle changes because of external factors, such as a pandemic of an infectious disease, the patient app may not provide similar efficacy to that achieved in the clinical trial. In order to maintain the efficacy of CureApp HT App, therefore, it is critical to update the output specifications in a timely manner so that they match the patient's trends and lifestyle.

Considering the clinical positioning of CureApp HT App as described later in Section "6.B Outline of the review conducted by PMDA," the risk of CureApp HT App for patients is negligible for the following reasons:

- CureApp HT App assists lifestyle modification in patients with hypertension that is a chronic disease.
- CureApp HT App is intended to be used as an add-on to patient's current treatment of hypertension under the supervision of a physician and is not intended to reduce the number or dose of drugs or the frequency of medical consultations.
- The effect of CureApp HT App on patients is dependent solely on [redacted] of patients themselves.

Therefore, any change in the output specifications will not pose any unacceptable risk to patients who are receiving hypertension treatment under the supervision of their treating physicians, though such change may impair the efficacy of the therapy to some extent, unless the change involves a change in the target patient populations or clinical positioning of CureApp HT App, or the treatment scheme of the patient app. It is rather important to update the output specifications in accordance with the times in order to maintain the clinical efficacy of CureApp HT App.

Based on the above, any change that does not involve a change in the target patient population or clinical positioning of CureApp HT App, or the treatment scheme of the patient app can be made to the output specifications of the patient app by submitting a minor change notification in accordance with Article 114-26 of the Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, provided that the applicant continues to verify the efficacy of CureApp HT App after approval and that a minor change notification for the change cannot be accepted if the efficacy is possibly decreased significantly.

The following approval condition will be imposed for CureApp HT App to be approved. The applicant is required to submit an annual report.

Approval Condition

The applicant is required to collect post-marketing information on the efficacy of the product annually after approval and to report it to the Pharmaceuticals and Medical Devices Agency to verify that the efficacy of the product is maintained.

To assess the maintained efficacy of CureApp HT App, the applicant should collect blood pressure measurement data (a patient outcome) and confirm whether patients have used CureApp HT App continuously. PMDA instructed the applicant to take the following measures.

Instructions

The applicant is required to submit annual reports to report data on user's blood pressure, the usage rate of CureApp HT App, and its post-marketing efficacy. The applicant is also required to take adequate management measures to assure the integrity of these data.

(d) The conformity of CureApp HT App to Article 12, which stipulates the requirements for software development life cycle for medical devices

PMDA's view:

As described earlier in Section "2.(1).B Outline of the review conducted by PMDA" and Section "2.(2).B Outline of the review conducted by PMDA," the software life cycle process has been implemented appropriately and CureApp HT App has been shown to operate adequately. The software development life cycle has been justified.

(e) The conformity of CureApp HT App to Article 17, which stipulates the general requirements for information provision to users through Information on Precautions, etc.:

PMDA's view

As described later in Section "6.B Outline of the review conducted by PMDA," to ensure the efficacy and safety of CureApp HT App, users should be fully informed of treatment with CureApp HT App before starting the therapy so that CureApp HT App is used in accordance with its clinical positioning. To that end, PMDA instructed the applicant to re-consider the intended use of CureApp HT App and take necessary measures, such as providing Information on Precautions, etc.

PMDA comprehensively reviewed the conformity of CureApp HT App to the Essential Principles, and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted data summarizing the risk management system and risk management activities implemented for CureApp HT App in accordance with JIS T 14971:2012 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

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

5. Manufacturing Process

5.A Summary of the data submitted

The applicant did not submit data on the manufacturing process of CureApp HT 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 manufacturing process of CureApp HT 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 of the "HERB[ii] Trial" (trial period, [redacted]) to support the clinical evaluation of CureApp HT App.

6.A.(1) Study design

The HERB trial was a prospective, multicenter, parallel-group, controlled study that evaluated the efficacy and safety of CureApp HT App in patients aged ≥20 and <65 years with Grade I or II essential hypertension who received no antihypertensive medication and were expected to be able to manage their hypertension by modifying lifestyle habits, such as diet and exercise. Table 2 shows the outline of the HERB trial.

The HERB trial evaluated an antihypertensive effect in the group of patients who received advice on lifestyle modifications in accordance with the Guidelines for the Management of Hypertension ("control group") versus the group of patients who used CureApp HT App in addition to receiving advice on lifestyle modifications in accordance with the Guidelines for the Management of Hypertension ("intervention group"). For the first 12 weeks post-enrollment, subjects received advice on lifestyle modifications alone (in combination with CureApp HT App in the intervention group). At Week 12, blood pressure was measured for 24 hours by ambulatory blood pressure monitoring (ABPM) to determine the mean of all effective values for 24 hours (24-hour ABPM). Of the subjects with 24-hour ABPM, subjects with mean systolic blood pressure (SBP) <130 mmHg continued on the non-pharmacological therapy for an additional 12 weeks (this group is referred to as the "non-pharmacological subgroup"). Subjects with mean SBP (24-hour ABPM) ≥130 mmHg at Week 12 started pharmacological therapy for an additional 12 weeks in principle (this group is referred to as the "pharmacological subgroup"). The type, dosage regimen, etc. of the drug to be prescribed were determined for each subject by the investigator or subinvestigator in accordance with the Guidelines for the Management of Hypertension and taking the subject's condition and complications into consideration.

Figure 2 shows the flow chart of the HERB trial.

[ii] HERB was the name of CureApp HT App used in the trial.

Table 2. Outline of the HERB trial

Item	Outline
Objective	The efficacy and safety of antihypertensive treatment at Week 12 was compared between the following 2 groups of patients with essential hypertension who received no prior antihypertensive pharmacological therapy: The group of patients receiving advice on lifestyle modifications in accordance with the Guidelines for the Management of Hypertension 2019 and using the investigational device (software as a medical device) and the group of patients receiving advice on lifestyle modifications alone in accordance with the Guidelines for the Management of Hypertension.
Type of the trial	Randomized, open-label, parallel-group, multicenter, Japanese clinical trial
Number of study sites	12 trial sites
Sample size	Number of treated subjects, 390 (199 in the intervention group, 191 in the control group)
Key inclusion criteria	1. Age of ≥20 and <65 years 2. Grade I or II essential hypertension (office SBP of 140-179 mmHg and/or diastolic blood pressure [DBP] of 90-109 mmHg) 3. Mean SBP (24-hour ABPM) ≥130 mmHg during the screening period 4. Patients receiving no prior antihypertensive pharmacological therapy (including patients receiving no antihypertensive pharmacological therapy for at least 3 months at the time of informed consent discussion) 5. Being able to use a smartphone[iii] and carry it on a daily basis 6. Being willing to undergo ABPM during the screening period, and at Weeks 12 and 24 7. Patients who should be treated mainly with lifestyle habit guidance without antihypertensive pharmacological therapy for approximately 12 weeks post-enrollment, according to the investigator's or subinvestigator's opinion
Key exclusion criteria	1. Grade III essential hypertension (office SBP ≥180 mmHg and/or DBP ≥110 mmHg) 2. Concurrent or previous secondary hypertension (including secondary hypertension that has to be excluded at screening) 3. Patients who are currently on any prohibited concomitant drug or therapy, or will be on such drug or therapy during the trial period 4. Patients for whom immediate initiation of pharmacological therapy is recommended in accordance with the Guidelines for the Management of Hypertension because of their medical history, concurrent diseases, or risk for cerebro-cardiovascular diseases. 5. Women who are pregnant or may possibly be pregnant, nursing women, or women who want to become pregnant during the clinical trial 6. Prior renal denervation using a catheter 7. Patients who have no smartphone or do not use or carry a smartphone on a daily basis 8. Patients who are currently participating in other clinical studies or have participated in any clinical study, including clinical research, using CureApp HT App, including patients allocated to control groups. Patients currently participating in other clinical studies can be enrolled in the HARB trial after ≥28 days have passed since the end of follow-up in the other studies. However, patients participating in other clinical studies of any antihypertensive therapies must meet Inclusion criterion No. 4. 9. Any patient's family member or partner has already participated in this clinical trial.
Primary endpoint	Change from baseline in mean SBP (24-hour ABPM) at Week 12 or study discontinuation before Week 12
Secondary endpoints	• Changes in mean SBP and DBP (24-hour ABPM, daytime ABPM, and nighttime ABPM) from baseline to Weeks 12 and 24 • Change in mean SBP and DBP (24-hour ABPM, daytime ABPM, and nighttime ABPM) from Week 12 to Week 24 • Changes in morning and evening home SBP and DBP from baseline to Weeks 12 and 24 • Change 12 in morning and evening home SBP and DBP from Week to Week 24 • Changes in morning and evening home pulse rate from baseline to Weeks 12 and 24 • Changes in office SBP and DBP from baseline to Weeks 12 and 24 • Change in pulse pressure (ABPM) from baseline to Week 24 • Change in mean pulse rate (24-hour ABPM) from baseline to Week 24 • Management rate* and efficacy rate** at Weeks 12 and 24 • Changes in body weight, BMI, and waist circumference from baseline to Weeks 12 and 24 • Changes in salt check sheet score from baseline to Weeks 12 and 24 • Changes in urinalysis levels[iv] from baseline to Weeks 12 and 24 • Usage rate of investigational device***
Safety endpoints	Adverse events and investigational device malfunctions

* Proportion of subjects whose morning and evening blood pressures meet the following goals, where home blood pressure is the mean for 7 days prior to a visit, exclusive of the day of visit (at least 5 days):
Goal 1, home SBP <135 mmHg and home DBP <85 mmHg
Goal 2, home SBP <125 mmHg and home DBP <75 mmHg

[iii] iOS or Android
[iv] Urinary Na (corrected for Cr) and urinary K (corrected for Cr)

** Proportion of subjects with a ≥5-mmHg decrease from baseline in mean SBP (24-hour ABPM)
*** Determined based on the following endpoints at Weeks 12 and 24

App usage rate	Percentage of days when the subject uses the patient app out of the 7 days prior to each visit
Progress of app educational program	Percentage of progress of app educational program in terms of knowledge acquisition (50%) and behavior experience (50%) regarding lifestyle changes recommended by the patient app
Home blood pressure measurement rate	Percentage of days when the subject measures blood pressure out of the 7 days prior to each visit
Behavior modification rate	Percentage of lifestyle behaviors that have been modified as self-evaluated by the subject out of all recommended behaviors
Self-monitoring rate	Percentage of days when the subject reviews their behaviors for the 7 days prior to each visit

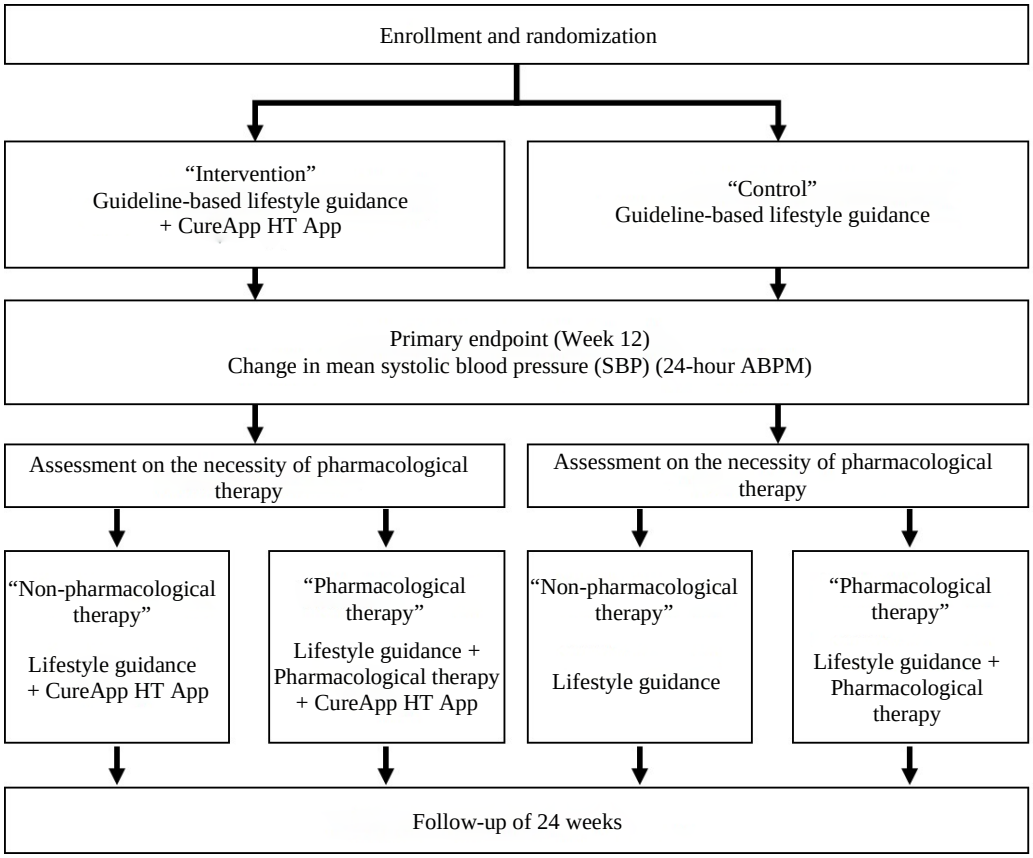


Figure 2. Flow chart of the HERB trial

The change in mean SBP (24-hour ABPM) from baseline to Week 12 was selected as the primary endpoint of the HERB trial because SBP is highly correlated to the risk of cerebro-cardiovascular events or target organ disorder, and this endpoint is recommended by related academic societies as an index of antihypertensive treatment for adult patients with essential hypertension.

Figure 3 shows the disposition of subjects in the HERB trial.

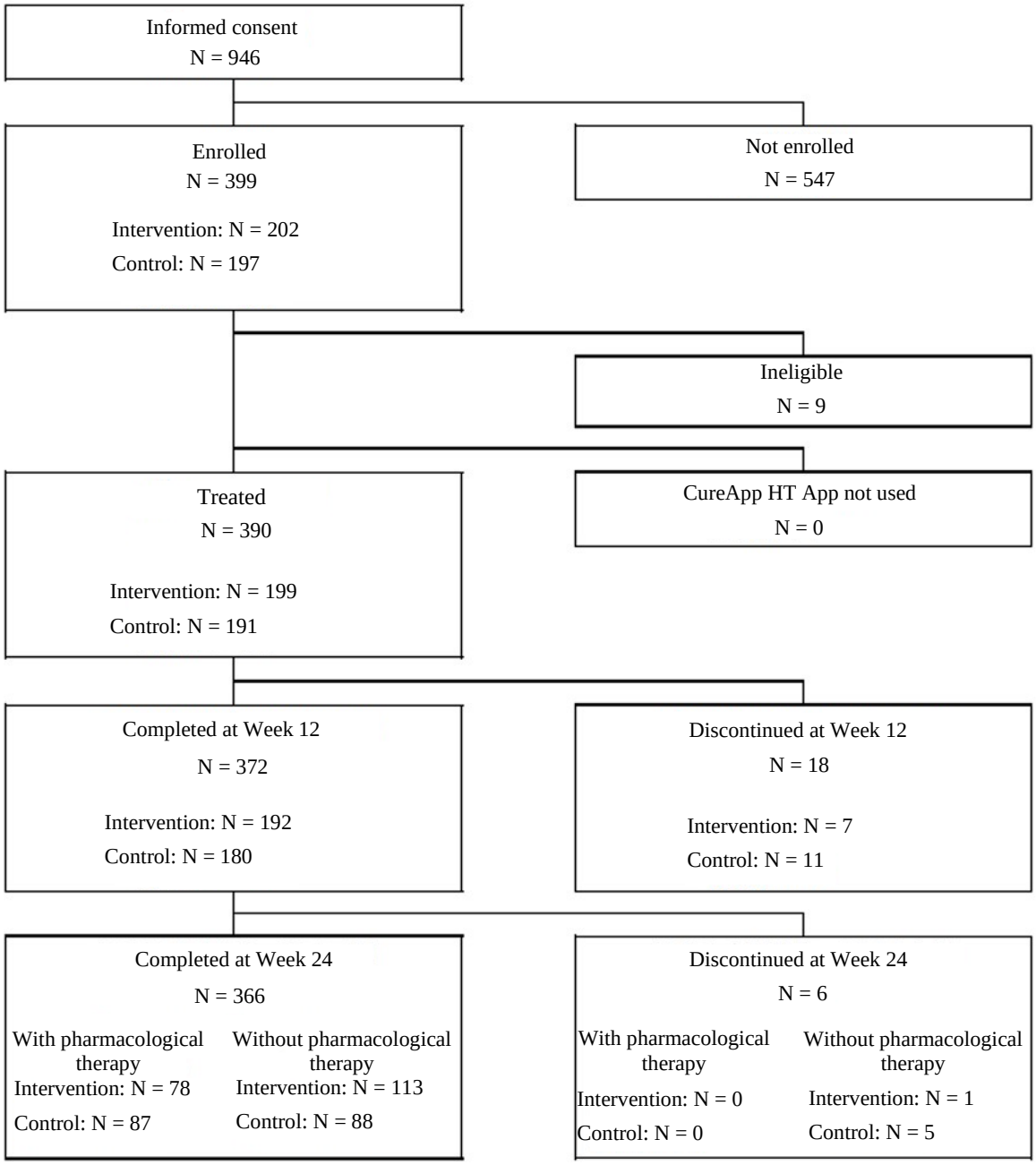


Figure 3. Disposition of subjects

6.A.(2) Patient characteristics

Table 3 shows a summary of the baseline demographics and characteristics of patients in the full analysis set (FAS) of the HERB trial.

Table 3. Summary of baseline demographics and characteristics of patients in FAS

Item	Intervention	Control
Age (mean ± standard deviation)	52.4 ± 8.06	52.0 ± 7.59
Sex	Female, 35 (17.6%) Male, 164 (82.4%)	Female, 43 (22.5%) Male, 148 (77.5%)
Height (mean ± standard deviation)	168.53 ± 7.387 cm	168.00 ± 8.101 cm
Weight (mean ± standard deviation)	73.27 ± 13.754 kg	72.95 ± 13.301 kg
BMI (mean ± standard deviation)	25.73 ± 4.065	25.76 ± 3.946
Waist circumference (mean ± standard deviation)	88.86 ± 10.615 cm	89.34 ± 10.493 cm
History of smoking	33 (16.6%)	29 (15.2%)
Dyslipidaemia	104 (52.3)	91 (47.6)
Diabetes mellitus	12 (6.0)	14 (7.3)
Previous cerebral haemorrhage	0 (0.0)	0 (0.0)
Previous cerebral infarction	0 (0.0)	0 (0.0)
Previous myocardial infarction	0 (0.0)	0 (0.0)
Non-valvular atrial fibrillation	2 (1.0)	1 (0.5)
Proteinuria	13 (6.5)	14 (7.3)
Previous or concurrent illness	157 (78.9)	150 (78.5)
Prior pharmacological treatment for essential hypertension	31 (15.6)	26 (13.6)

6.A.(3) Trial results

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

The HERB trial was conducted to verify the hypothesis that the intervention is superior to the control. The primary endpoint was the change in mean SBP (24-hour ABPM) from baseline to Week 12. In the FAS, the change in mean SBP (24-hour ABPM) from baseline to Week 12 or study discontinuation was −6.9 ± 10.70 mmHg in the intervention group and −4.7 ± 10.32 mmHg in the control group. A between-group comparison of the primary endpoint was performed using an analysis of the covariance model including group (intervention or control), study site, and prior pharmacological treatment as factors, baseline mean SBP (24-hour ABPM) as a covariant. The least squares mean ± standard error was −4.9 ± 1.23 mmHg in the intervention group and −2.5 ± 1.30 mmHg in the control group, with an estimate of the between-group difference in the change (change in the intervention group − change in the control group) of −2.4 mmHg (95% CI, −4.5 to −0.3 mmHg). The change in the intervention group was significantly greater than that in the control group.

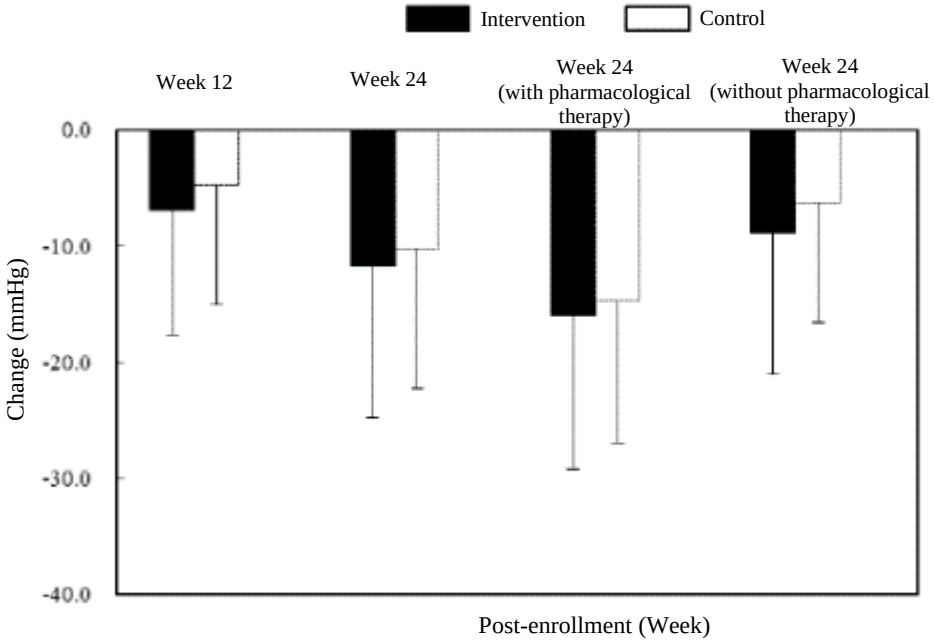
6.A.(3).2) Secondary endpoints

The secondary endpoints of the trial included mean daytime and nighttime SBP and diastolic blood pressure (DBP) measured by ABPM (daytime ABPM and nighttime ABPM, respectively), morning and evening home SBP and DBP, and SBP and DBP measured at office in a sitting position at rest (office SBP and DBP).

The results of these endpoints are summarized below.

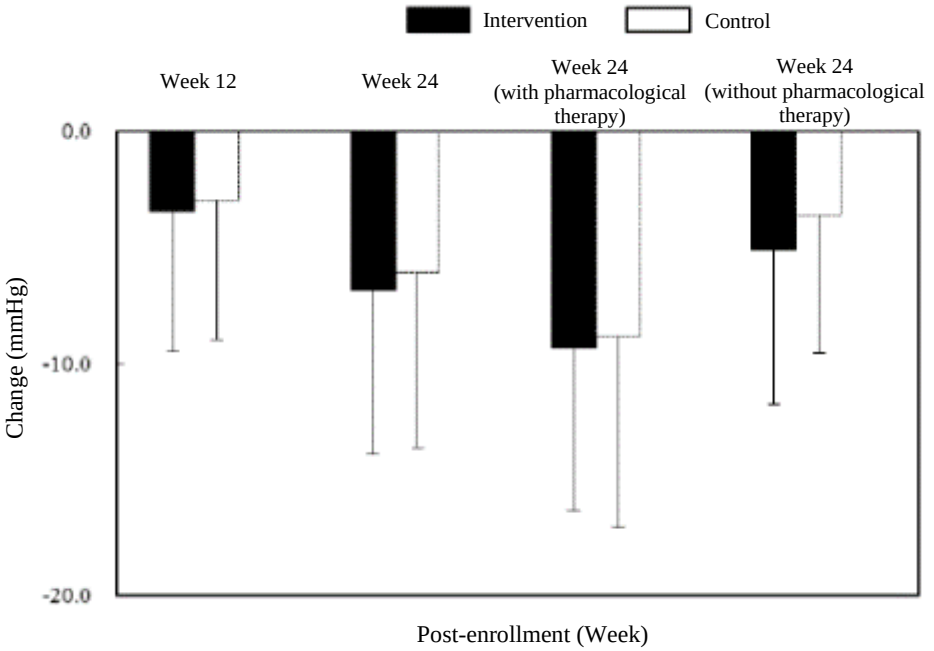
(a) ABPM

Figures 4 to 9 show the changes in mean SBP and DBP (24-hour ABPM, daytime ABPM, and nighttime ABPM) from baseline to Weeks 12 and 24.



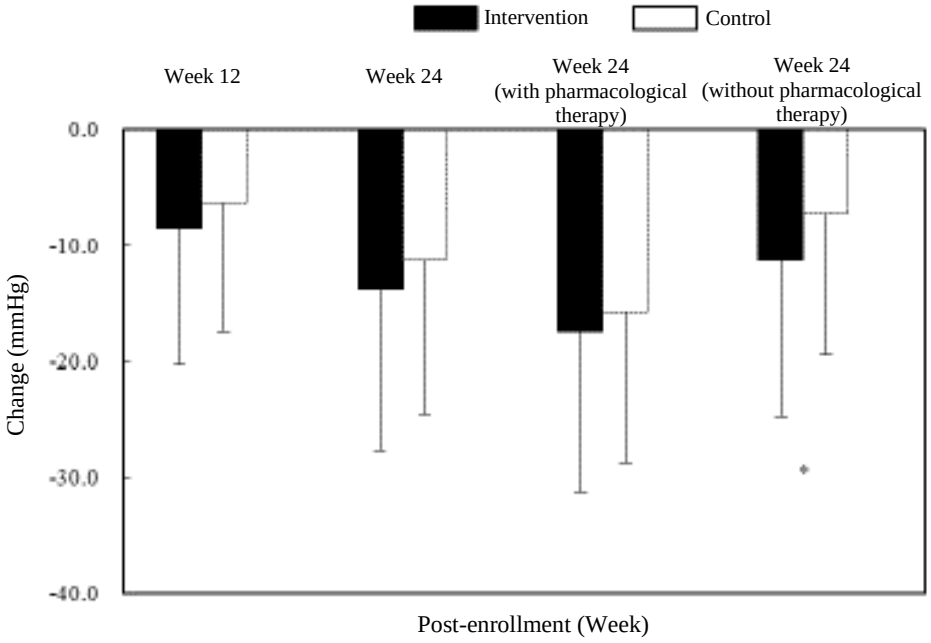
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 4. Change in mean SBP (24-hour ABPM)



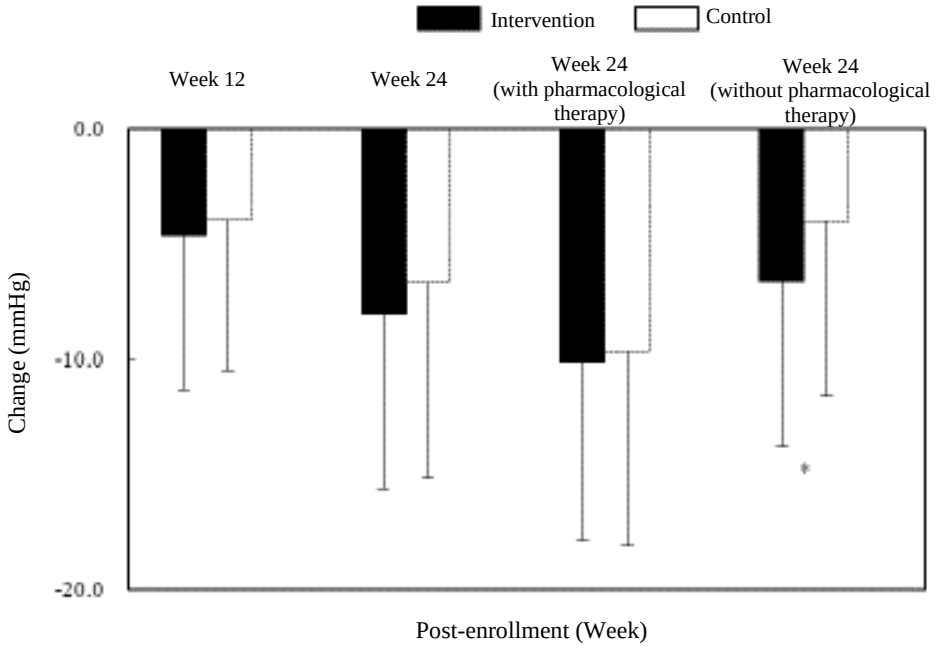
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 5. Change in mean DBP (24-hour ABPM)



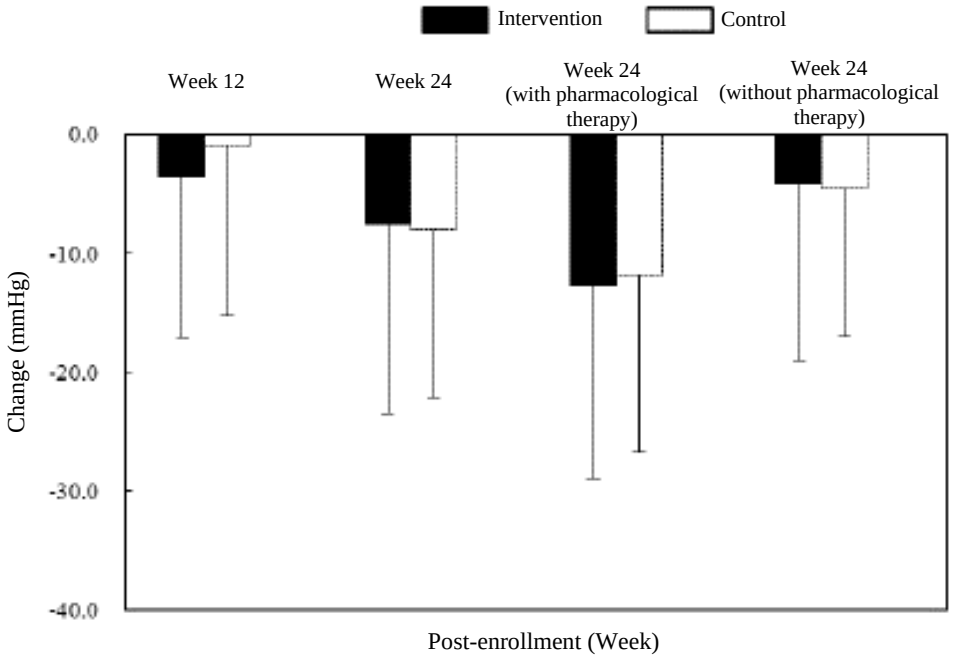
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 6. Change in mean SBP (daytime ABPM)



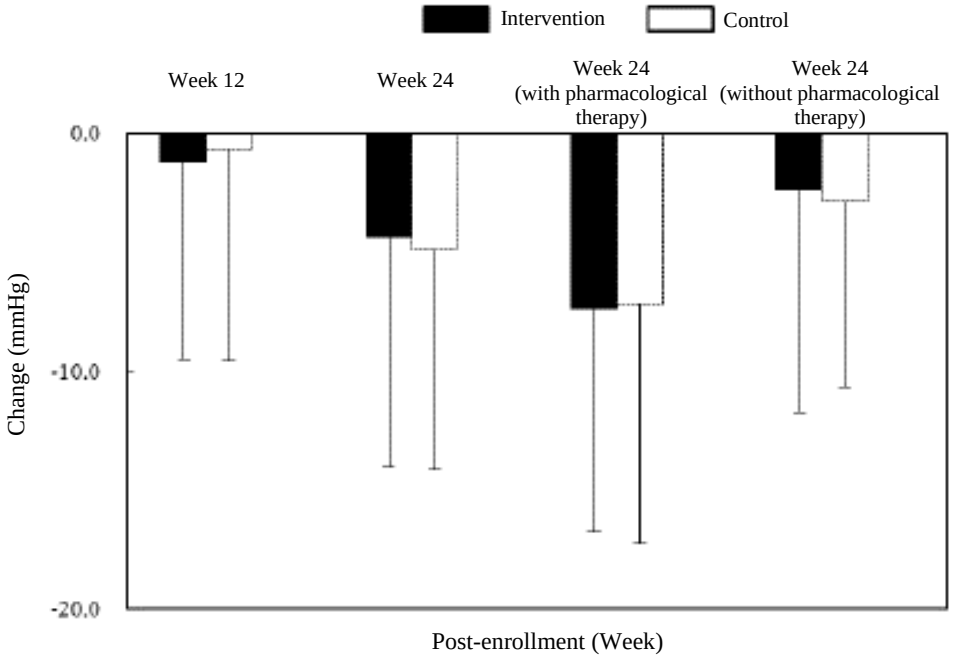
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 7. Change in mean DBP (daytime ABPM)



* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 8. Change in mean SBP (nighttime ABPM)

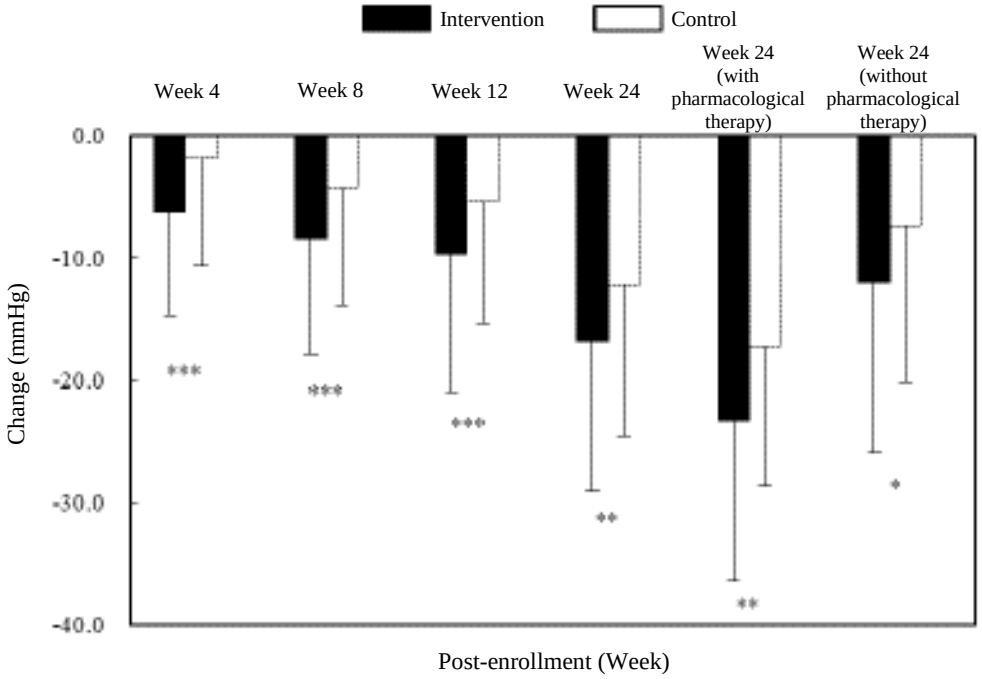


* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 9. Change in mean DBP (nighttime ABPM)

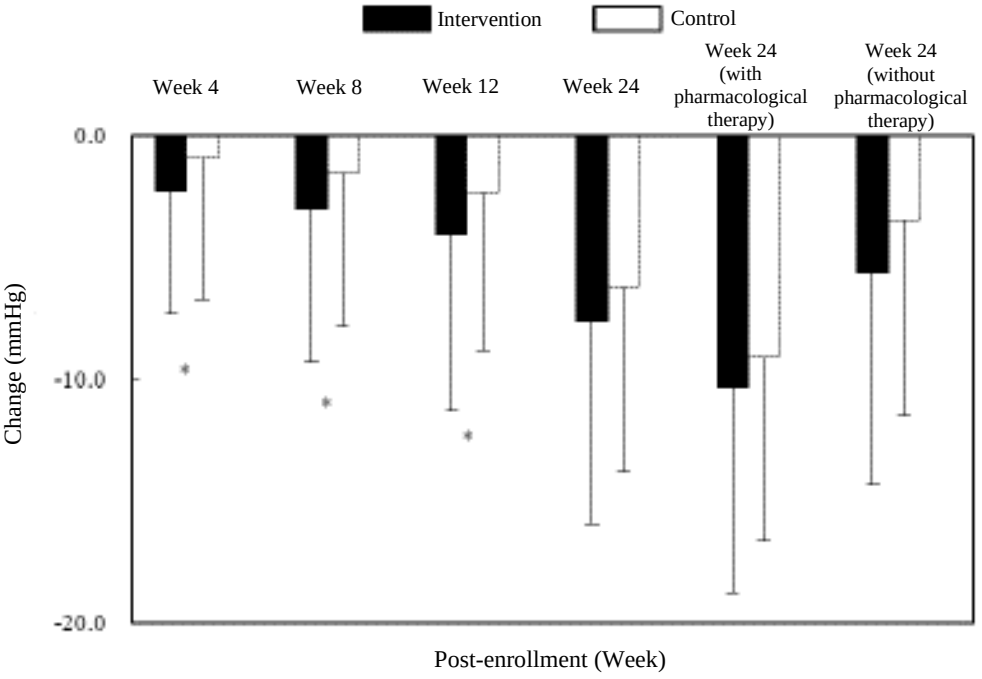
(b) Home blood pressure

Figures 10 to 13 show the change from baseline in morning and evening home SBP and DBP.



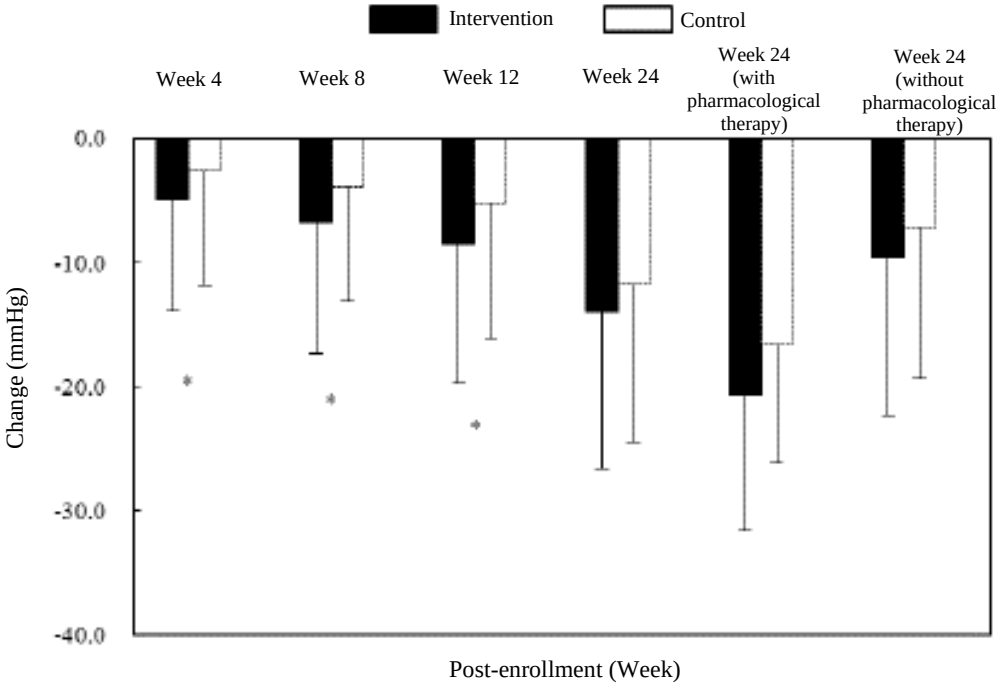
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 10. Change in mean home SBP (morning)



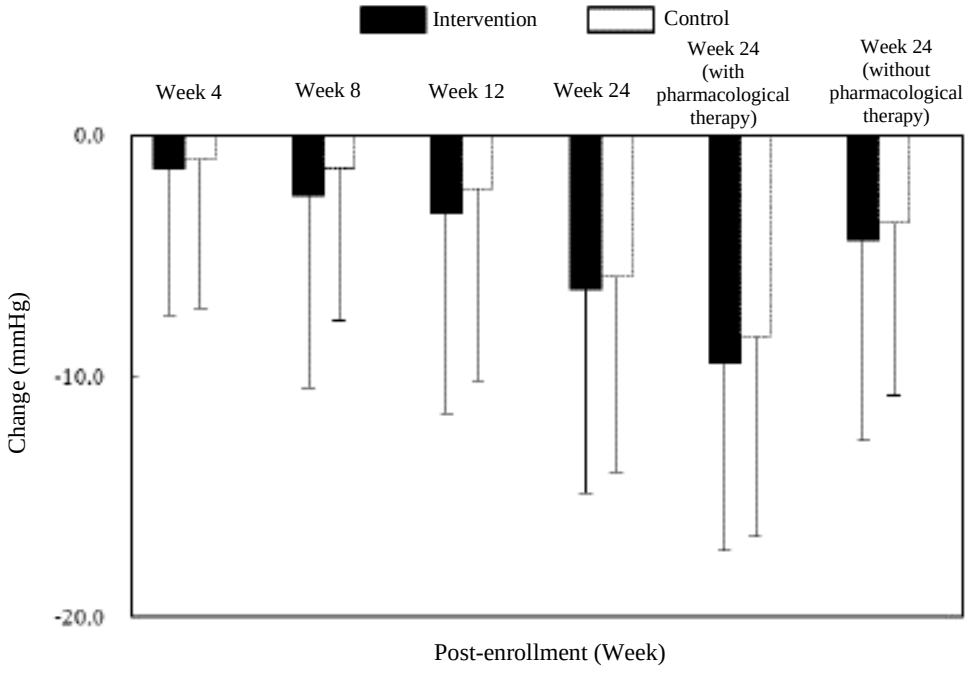
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 11. Change in mean home DBP (morning)



* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 12. Change in mean home SBP (evening)

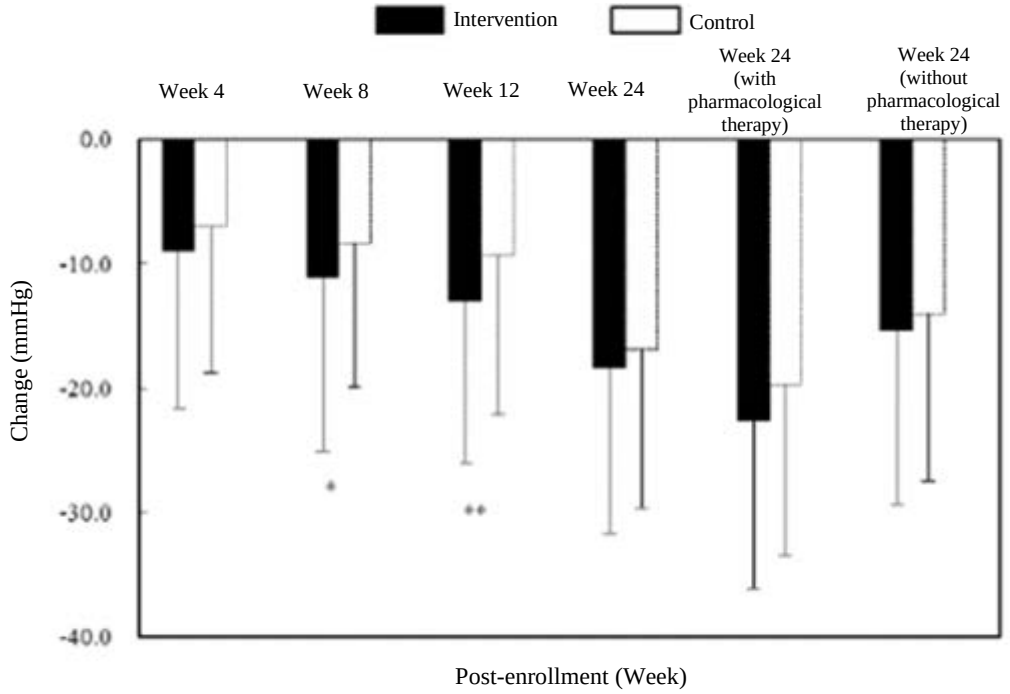


* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 13. Change in mean home DBP (evening)

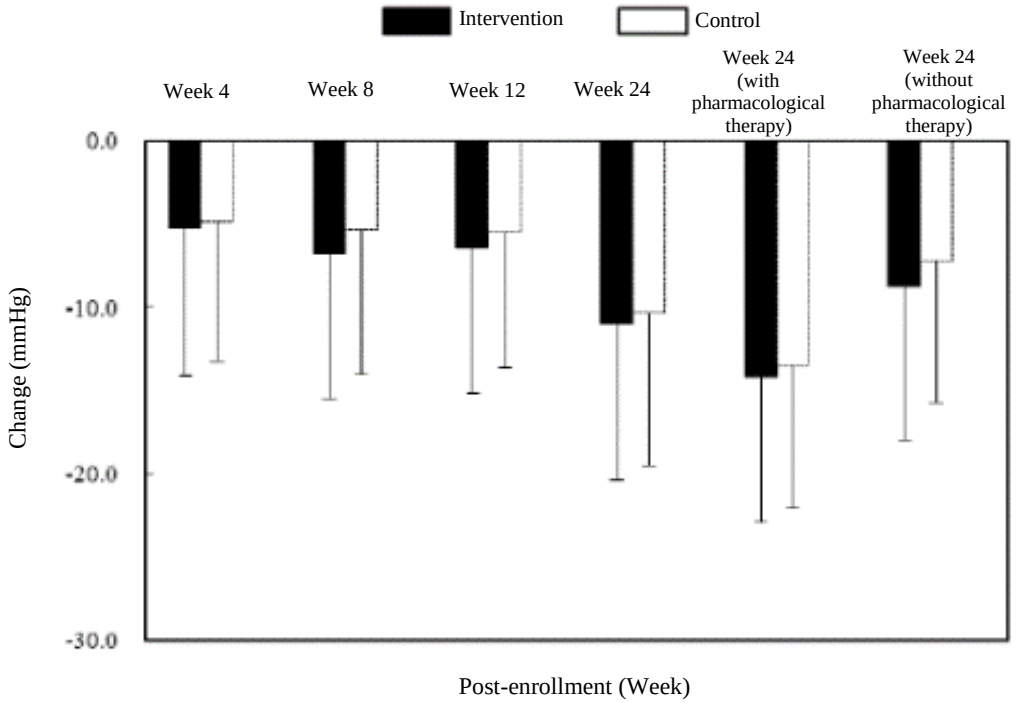
(c) Office blood pressure

Figures 14 and 15 show the change from baseline in office SBP and DBP, respectively.



* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 14. Change in mean office SBP



* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 15. Change in mean office DBP

(d) Management rate and efficacy rate

The management rate was defined as the proportion of subjects whose morning and evening home blood pressure values both met the prespecified goals, where home blood pressure is the mean for 7 days prior to a visit, exclusive of the day of the visit (at least 5 days). The efficacy rate was defined as the proportion of subjects with a ≥5-mmHg decrease from baseline in mean SBP (24-hour ABPM). Table 4 shows the results of the management rate and efficacy rate in the HERB trial.

Table 4. Management rate and efficacy rate

			Management rate		Efficacy rate
			Goal 1	Goal 2	
Week 12	Intervention		22.2% (39/176)	2.3% (4/176)	59.0% (105/178)
	Control		10.4% (18/173)	1.2% (2/173)	50.6% (86/170)
Week 24	Overall	Intervention	35.1% (59/168)	6.5% (11/165)	72.2% (127/176)
		Control	19.0% (31/163)	0.6% (1/163)	66.3% (106/160)
	With pharmacological therapy	Intervention	37.7% (26/69)	4.3% (3/69)	82.9% (58/70)
		Control	17.9% (15/84)	1.2% (1/84)	82.9% (63/76)
	Without pharmacological therapy	Intervention	33.3% (33/99)	8.1% (8/99)	65.1% (69/106)
		Control	20.3% (16/79)	0.0% (0/79)	51.2% (43/84)

* To calculate the management rate and efficacy rate, the number of all subjects having necessary measurements for calculation of each parameter is used as the denominator.

(e) Usage rate of investigational device

Table 5 shows the usage rate of the patient app in the intervention group of the HERB trial.

Table 5. Usage rate of the patient app in the intervention group

		Week 12	Week 24		
			Overall	With pharmacological therapy	Without pharmacological therapy
	N	192	190	78	112
App usage rate (%)	Mean	98.06	96.24	97.80	95.15
	Standard deviation	7.351	13.512	9.524	15.654
	Minimum	42.8	0.0	42.8	0.0
	Maximum	100.0	100.0	100.0	100.0
Educational program progress rate (%)	Mean	70.95	79.24	78.79	79.54
	Standard deviation	13.071	9.371	9.820	9.077
	Minimum	3.5	50.0	50.0	50.0
	Maximum	93.2	98.2	97.9	98.2
Behavior modification rate (%)	Mean	41.93	56.43	55.54	57.04
	Standard deviation	19.522	18.111	18.992	17.531
	Minimum	0.0	0.0	0.0	0.0
	Maximum	86.4	96.1	93.5	96.1
Self-monitoring rate (%)	Mean	83.77	82.24	83.87	81.11
	Standard deviation	26.461	28.063	25.684	29.668
	Minimum	0.0	0.0	0.0	0.0
	Maximum	100.0	100.0	100.0	100.0

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

Table 6 shows adverse events occurring in the HERB trial. Adverse event data were collected through records on the patient app and hearings during medical consultations in the intervention group, or through hearings during medical consultations in the control group. Adverse events occurred more frequently in the intervention group (91 subjects, 45.5%) than in the control group (54 subjects, 27.8%) up to Week 24.

One subject in the intervention group had a non-fatal, serious adverse event. The subject was a 6[redacted]-year old man with no medical history, and had concurrent dyslipidaemia and obesity. Moderate pulmonary embolism occurred on Day 5, which required hospitalization for treatment. The event resolved 175 days after its onset. The subject with a non-fatal, serious adverse event in the control group was a 6[redacted]-year old man with no medical history, and had concurrent T-wave depression, hyperuricaemia, and dyslipidaemia. The subject requested withdrawal from the trial on Day 84 because of treatment of lymphoma. Since this subject was withdrawn from the trial, the severity of this adverse event was assessed as severe according to the protocol-defined criteria.

Severe adverse events other than the serious adverse events were reported in 3 subjects in the control group. The first subject was a 5[redacted]-year old man with no medical history, and had concurrent hepatic impairment, hyperuricaemia, insomnia, and pollinosis. The subject experienced severe visual impairment on Day 144 and requested withdrawal from treatment. The event did not resolve by 8 days after its onset. The second subject was a 6[redacted]-year old man with no medical history, and had concurrent pollinosis. Intracranial aneurysm occurred on Day 105, which resulted in withdrawal from the trial at the discretion of the treating physician. The event did not resolve by 33 days after its onset. The third subject was a 5[redacted]-year old man with no medical history or concurrent illness. The subject experienced asthma on Day 101 and requested withdrawal from the trial.

All of the adverse events occurring in the HERB trial were considered unrelated to CureApp HT App.

Table 6. Adverse events reported up to Week 24

	Intervention N = 200		Control N = 194	
	Number of events	n (%)	Number of events	n (%)
Adverse events	228	91 (45.5)	84	54 (27.8)
Death	0	0 (0)	0	0 (0)
Non-fatal, serious adverse events	1	1 (0.5)	1	1 (0.5)
Severe adverse events other than serious adverse events	0	0 (0.0)	3	3 (1.5)
Adverse events leading to discontinuation of the trial or investigational device	1	1 (0.5)	4	4 (2.1)

6.A.(3).4) Malfunctions

Table 7 shows malfunctions occurring in the HERB trial. A total of 57 “unexpected malfunctions” occurred up to Week 24 in 48 of 200 subjects (24.0%). Table 8 shows the details of the malfunctions.

Neither “serious malfunction” nor” malfunction possibly resulting in trial-related injury” was reported.

Table 7. Malfunctions reported up to Week 24 (overall population, N = 200)

	Number of events	n (%)
Malfunctions	57	48 (24.0)
Serious malfunctions	0	0 (0.0)
Unexpected malfunctions	57	48 (24.0)
Malfunctions possibly resulting in trial-related injury	0	0 (0.0)

Table 8. Details of malfunctions (N = 57)

Malfunction	Number of malfunctions (%)
Poor connection to Bluetooth and poor pairing of CureApp HT App and a sphygmomanometer	36 (63.2)
Content not displayed properly	9 (15.8)
Unable to input data properly	6 (10.5)
Unable to launch the app	3 (5.3)
Other operation failures	3 (5.3)

6.B Outline of the review conducted by PMDA

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

6.B.(1) Clinical positioning of CureApp HT App

The applicant's explanation about the clinical positioning of CureApp HT App:

CureApp HT App is intended to be used as an add-on to current standard treatment. CureApp HT App is expected to improve lifestyle modifications in terms of quality and extent. CureApp HT App helps physicians to collect patient's information at home effectively, which is difficult to collect. This will result in better medical management. CureApp HT App may partially replace current clinical practice.

CureApp HT App is also expected to reduce the number or dose of drugs, and the frequency of hospital visits, as well as to improve the quality of medical care because it can provide patients with an opportunity of treatment outside of hospital visits, which is impossible through conventional approaches.

PMDA's view:

It is understandable that the applicant positioned CureApp HT App as an add-on to standard treatment to achieve a higher antihypertensive effect than that of the standard treatment alone. However, the HERB trial was not designed to investigate whether CureApp HT App could reduce the number or dose of drugs or the frequency of hospital visits, but to evaluate the efficacy and safety of CureApp HT App when it was used within the scope of standard treatment recommended by the Guidelines for the Management of Hypertension. The HERB trial did not evaluate CureApp HT App for the clinical positioning explained by the applicant, although CureApp HT App may potentially reduce the number or dose of drugs, or the frequency of hospital visits as a result of successful lifestyle modifications with the use of CureApp HT App and consequent better blood pressure management.

In view of the above points, currently, CureApp HT App should be used as an add-on to lifestyle guidance that is practiced as a standard of care, i.e., CureApp HT App should be positioned as an adjunctive treatment that is expected to help patients make lifestyle modifications necessary for hypertension treatment. On the basis of the above review, PMDA instructed the applicant to re-discuss

the clinical positioning of CureApp HT App and to change its brand name and intended use based on its clinical positioning.

The applicant's response:
The applicant decided to change the intended use of CureApp HT App to clarify that CureApp HT App would be used as an adjunctive treatment, but planned not to change the brand name of CureApp HT App. If the brand name of CureApp HT App includes "treatment app," it might mislead its patient users that CureApp HT App alone can complete their hypertension treatment. In order to prevent this misunderstanding, the users should be informed to ensure that CureApp HT App is used in combination with routine clinical practice only under the supervision of physicians.

To this end, an app lock feature is incorporated in the patient app to prevent patients from using it if patients do not receive a medical consultation from their treating physicians for an extended period of time. Some steps are required to use the app lock feature. [redacted]. The duration of management period will be 128 days or a shorter period determined by physicians. [redacted].

The above approach allows CureApp HT App to be used only under the supervision of physicians and prevents misunderstanding by patients.

PMDA concluded that there was no particular problem with the applicant's response.

6.B.(2) Efficacy and safety

6.B.(2).1) Degree of antihypertensive effect

The applicant's explanation about the clinical significance of the degree of antihypertensive effect of CureApp HT App based on the results of the HERB trial:
The between-group difference in SBP (24-hour ABPM) of 2.4 mmHg as shown by the analysis of the primary endpoint is correlated to a 10.7% decrease in the risk of cardiovascular events for the risk of developing cerebro-cardiovascular diseases and a 10.1% decrease in the risk of cerebro-cardiovascular death (risk of blood pressure-related death).[8,9] In the control group of the HERB trial, the proportion of subjects who measured their blood pressure using a sphygmomanometer was higher than that of patients in clinical practice. The control group of the clinical trial showed a better management of hypertension than clinical practice. In the clinical setting, therefore, CureApp HT App may provide a much higher antihypertensive effect than that seen in the HERB trial. Secondary endpoints also showed a higher antihypertensive effect in the intervention group than in the control group. In particular, the intervention group achieved a more substantial decrease in home blood pressure than the control group.

[redacted]

PMDA's view:
The HERB trial showed a higher antihypertensive effect in the intervention group than in the control group. The estimated difference in the degree of antihypertensive effect between the intervention group and the control group was 2.4 mmHg (24-hour ABPM), which could be a clinically significant difference in preventing cerebro-cardiovascular events and related deaths.[10]

The management rate shown in Table 4 indicates that the proportion of patients achieving their preset blood pressure goals tended to be higher in the intervention group than in the control group. The preset blood pressure goals are classified as high or normal blood pressure. CureApp HT App is expected to help many patients keep lifestyle modifications and low-risk blood pressure levels. Since the effect of CureApp HT App is [redacted], the intervention is basically limited to the behaviors of patients themselves. CureApp HT App is, therefore, not considered to constitute any particular risk to patients as long as it is used as an aid to help patients modify their lifestyle habits under the supervision of their treating physicians after the patients are fully informed of the use of CureApp HT App.

On the basis of the above and taking the risk of CureApp HT App into consideration, PMDA concluded that the submitted data has demonstrated the clinical usefulness of CureApp HT App.

6.B.(2).2) Long-term effect
CureApp HT App can be used unlimitedly by patients who need to improve their lifestyle habits.

The applicant's explanation about the long-term effect of CureApp HT App:
To evaluate the long-term effect of CureApp HT App, the change in blood pressure from Week 12 to Week 24 was analyzed. After Week 12, subjects were divided into 2 groups: "non-pharmacological subgroup" and "pharmacological subgroup." The data were analyzed separately in these subgroups because the degree of antihypertensive effect should be interpreted differently between these subgroups.

Tables 9 and 10 show the change in blood pressure from Week 12 to Week 24 in the "non-pharmacological subgroup" in the HERB trial. Neither group had a substantial change in blood pressure. The "non-pharmacological subgroup" consisted of subjects with SBP (24-hour ABPM) <130 mmHg and subjects requiring no pharmacological therapy at the physician's discretion at Week 12. These subjects achieved an adequate decrease in blood pressure through lifestyle modifications alone at Week 12, and were therefore unlikely to show additional antihypertensive effect through lifestyle modifications after Week 12. In the "non-pharmacological subgroup," 1 of 114 subjects (0.88%) in the intervention group and 5 of 93 subjects (5.4%) in the control group were withdrawn from the study. These results suggest that CureApp HT App would make continuous treatment easier than the standard treatment.

Tables 11 and 12 show the change in blood pressure from Week 12 to Week 24 in the "pharmacological subgroup" in the HERB trial. The "pharmacological subgroup" consisted of subjects

with SBP (24-hour ABPM) ≥130 mmHg and subjects requiring pharmacological therapy at the physician's discretion at Week 12. The intervention group had a comparable or greater decrease in blood pressure, except for nighttime ABPM blood pressure, than the control group. In addition, the blood pressure at Week 12 in the intervention group was lower than that in the control group. These results suggest the possibility of a higher antihypertensive effect observed in the intervention group than the control group.

Table 9. Non-pharmacological subgroup – change in SBP from Week 12 to Week 24 and between-group difference

[mmHg]	Change in SBP Intervention	Change in SBP Control	Between-group difference in change
24-hour ABPM	0.8 ± 9.29	1.3 ± 9.52	−0.5
Daytime ABPM	0.6 ± 10.63	1.9 ± 9.98	−0.7
Nighttime ABPM	1.1 ± 11.37	−0.1 ± 11.69	1.2
Home blood pressure (morning)	−1.8 ± 7.59	−0.8 ± 9.09	−1.0
Home blood pressure (evening)	−0.5 ± 8.55	−1.8 ± 8.76	1.3
Office blood pressure	−0.4 ± 11.39	−0.7 ± 12.01	0.3

Table 10. Non-pharmacological subgroup – change in DBP from Week 12 to Week 24 and between-group difference

[mmHg]	Change in DBP Intervention	Change in DBP Control	Between-group difference in change
24-hour ABPM	0.1 ± 5.23	1.1 ± 5.44	−1.0
Daytime ABPM	0.2 ± 5.89	1.6 ± 5.87	−1.4
Nighttime ABPM	0.1 ± 7.39	0.0 ± 6.70	0.1
Home blood pressure (morning)	−1.4 ± 5.59	−0.4 ± 5.51	−1.0
Home blood pressure (evening)	−0.7 ± 6.26	−1.5 ± 6.50	−0.8
Office blood pressure	−1.0 ± 7.36	−0.3 ± 6.30	−0.7

Table 11. Pharmacological subgroup – change in SBP from Week 12 to Week 24 and between-group difference

[mmHg]	Change in SBP Intervention	Change in SBP Control	Between-group difference in change
24-hour ABPM	−13.4 ± 11.87	−13.3 ± 12.12	−0.1
Daytime ABPM	−14.1 ± 12.89	−12.6 ± 12.41	−1.5
Nighttime ABPM	−11.1 ± 16.17	−14.7 ± 14.53	3.6
Home blood pressure (morning)	−14.4 ± 10.69	−12.2 ± 10.72	−2.2
Home blood pressure (evening)	−14.9 ± 9.78	−12.3 ± 12.63	−2.6
Office blood pressure	−12.7 ± 12.87	−14.4 ± 12.6	1.7

Table 12. Pharmacological subgroup – change in DBP from Week 12 to Week 24 and between-group difference

[mmHg]	Change in DBP Intervention	Change in DBP Control	Between-group difference in change
24-hour ABPM	−8.4 ± 7.05	−7.9 ± 7.60	−0.5
Daytime ABPM	−8.8 ± 7.81	−7.9 ± 7.67	−0.9
Nighttime ABPM	−7.4 ± 9.45	−8.6 ± 9.70	0.8
Home blood pressure (morning)	−7.5 ± 5.79	−6.9 ± 6.37	−0.6
Home blood pressure (evening)	−8.0 ± 6.62	−6.9 ± 8.51	−1.1
Office blood pressure	−9.7 ± 8.82	−9.3 ± 9.23	−0.4

PMDA's view:

The difference in the change in SBP (24-hour ABPM) from Week 12 to Week 24 between the "pharmacological subgroup" and the "non-pharmacological subgroup" tended to be smaller than that in the primary endpoint. From this result, it is difficult to conclude that CureApp HT App continues to

have a higher antihypertensive effect than that of the standard treatment for an extended period of time. However, the intervention group achieved a significantly higher antihypertensive effect than the control group at Week 12. Given this, the fact that the two groups had a similar change in blood pressure from Week 12 to Week 24 suggests that CureApp HT App provided an early antihypertensive effect and maintained its effect. If CureApp HT App provides an early antihypertensive effect by helping patients modify their lifestyle habits and at least maintains a similar antihypertensive effect to the standard treatment, the long-term use of CureApp HT App should not be denied even taking its risk into consideration.

In summary, although whether the long-term use of CureApp HT App provides a similar add-on effect to that seen in the primary endpoint remains unknown, the long-term use of CureApp HT App is expected to provide a similar sustainable antihypertensive effect to that of the standard treatment. On the other hand, patients, especially those requiring no pharmacological therapy, may fail to receive the standard treatment, such as blood pressure management under the supervision of physicians, which is usually required in clinical practice to manage hypertension, during the long-term use of CureApp HT App. This is the risk of its long-term use. PMDA instructed the applicant to provide adequate precautions to ensure that CureApp HT App is used under the supervision of physicians and to clarify the clinical positioning of CureApp HT App to patients, i.e., its users.

The applicant responded that as described earlier, they planned to incorporate an app lock feature in the patient app to prevent patients from using it if patients do not receive a medical consultation from their treating physicians for an extended period of time.

PMDA concluded that there is no need to impose a particular limit on the duration of treatment with CureApp HT App because its long-term use is unlikely to pose a substantial risk to users as long as it is used under the supervision of physicians.

6.B.(3) Target patient population

The applicant submitted an application for CureApp HT App, which was intended to be used in patients aged ≥7 years with essential hypertension, including those with Grade III hypertension. Since the patient population included in the HERB trial differed from the target patient population of CureApp HT App, its efficacy and safety were reviewed in the following patient populations.

1) Patients with Grade III hypertension
2) Elderly patients
3) Pediatric patients

6.B.(3).1) Patients with Grade III hypertension

The HERB trial enrolled patients with Grade I and II hypertension as diagnosed according to the office blood pressure-based criteria. Patients with Grade III hypertension were excluded from the trial according to the exclusion criteria. PMDA asked the applicant to explain the efficacy and safety of CureApp HT App in this patient population.

The applicant's explanation:

The HERB trial included patients with Grade III hypertension as diagnosed according to the home blood pressure-based criteria (SBP ≥160 mmHg and/or DBP ≥110 mmHg) during the screening period. Tables 13 and 14 shows the results of blood pressure at Week 12 in the above patient population. All SBP endpoints showed a higher antihypertensive effect in the intervention group than in the control group.

To reduce the risk associated with exercise therapy, which may impose an excessive load on the body, the patient app is designed to advise patients to ask their physicians about possible exercise restrictions and propose stretching, not walking. Patients requiring precautions for exercise are warned through the Information on Precautions, etc. The risk of using CureApp HT App in patients with Grade III hypertension appears to be acceptable because no adverse event associated with the use of CureApp HT App was reported in the HERB trial.

Table 13. Blood pressure data in patients with Grade III hypertension as diagnosed according to the home blood pressure-based criteria (SBP, Week 12)

		Intervention			Control			Between-group difference
		No. of subjects	Measured value	Difference	No. of subjects	Measured value	Difference	
ABPM (24 hour)	Baseline	33	152.7 ± 12.8	−5.7 ± 11.8	33	154.7 ± 10.8	−3.3 ± 12.8	−2.4
	Week 12	28	146.9 ± 11.5		26	149.7 ± 13.2		
ABPM (daytime)	Baseline	33	159.7 ± 11.4	−8.1 ± 12.9	33	161.5 ± 11.2	−5.1 ± 11.7	−3.0
	Week 12	28	151.9 ± 11.7		26	154.2 ± 12.2		
ABPM (nighttime)	Baseline	33	138.9 ± 17.5	−1.3 ± 14.8	33	139.5 ± 16.2	2.8 ± 18.1	−4.1
	Week 12	28	136.4 ± 15.9		26	141.5 ± 18.5		
Home blood pressure (morning)	Baseline	33	166.5 ± 8.1	−16.9 ± 14.1	33	167.0 ± 6.7	−10.6 ± 11.2	−6.3
	Week 12	30	149.9 ± 15.7		30	156.2 ± 10.7		
Home blood pressure (evening)	Baseline	31	153.7 ± 11.5	−12.7 ± 11.9	30	158.6 ± 13.7	−8.1 ± 10.6	−4.6
	Week 12	27	140.3 ± 14.2		25	149.2 ± 15.3		
Office blood pressure	Baseline	33	159.1 ± 9.2	−11.1 ± 14.3	33	157.8 ± 10.1	−7.9 ± 13.4	−3.2
	Week 12	31	148.6 ± 14.9		30	149.1 ± 12.4		

Table 14. Blood pressure data in patients with Grade III hypertension as diagnosed according to the home blood pressure-based criteria (DBP, Week 12)

		Intervention			Control			Between-group difference
		No. of subjects	Measured value	Difference	No. of subjects	Measured value	Difference	
ABPM (24 hour)	Baseline	33	98.6 ± 7.8	−1.9 ± 6.1	33	98.5 ± 8.9	−2.5 ± 6.9	0.6
	Week 12	28	96.7 ± 7.9		26	94.7 ± 9.6		
ABPM (daytime)	Baseline	33	103.0 ± 7.9	−3.5 ± 7.4	33	102.4 ± 9.4	−3.3 ± 6.7	−0.2
	Week 12	28	99.6 ± 7.7		26	97.6 ± 9.7		
ABPM (nighttime)	Baseline	33	89.9 ± 10.4	1.5 ± 8.9	33	90.1 ± 11.2	0.3 ± 9.8	1.2
	Week 12	28	90.9 ± 11.2		26	89.3 ± 11.7		
Home blood pressure (morning)	Baseline	33	105.3 ± 7.7	−8.1 ± 8.9	33	102.5 ± 8.7	−10.6 ± 11.2	2.5
	Week 12	30	97.6 ± 10.4		30	98.9 ± 10.2		
Home blood pressure (evening)	Baseline	31	96.4 ± 10.3	−6.7 ± 10.7	30	94.3 ± 9.0	−1.6 ± 8.4	−5.6
	Week 12	27	89.4 ± 10.0		25	91.3 ± 10.9		
Office blood pressure	Baseline	33	102.4 ± 5.4	−5.2 ± 8.6	33	101.7 ± 6.0	−3.7 ± 6.8	−1.5
	Week 12	31	97.7 ± 10.2		30	98.0 ± 8.0		

PMDA's view:

Patients with Grade III hypertension as diagnosed according to the home blood pressure-based criteria in the intervention group achieved a higher antihypertensive effect than patients in the control group. However, the HERB trial enrolled patients with Grade I or II hypertension as diagnosed according to the office blood pressure-based criteria. In addition, only limited number of patients with Grade III hypertension were enrolled in the HERB trial. This precludes evaluating the efficacy of CureApp HT App in severe patients based on the results of the trial.

However, lifestyle modifications are also recommended to more severe patients. CureApp HT App is expected to provide some antihypertensive effect although the magnitude of its clinically significant add-on effect is unknown. Exercise that puts an excessive load on the body may impose a risk to patients with Grade III hypertension, but patients themselves will be able to avoid the risk associated with exercise if they understand advice from the patient app. This is because (i) CureApp HT App is designed to propose stretching to patients who need to be careful about exercise; and (ii) hypertension is diagnosed and treated after assessing cerebro-cardiovascular risk factors, cerebro-cardiovascular complications, etc., and physicians will warn patients about the risk associated with strenuous exercise, if any. Some patients with Grade III hypertension require immediate pharmacological therapy. CureApp HT App may delay the start of conventional treatment in these patients, which is clearly a risk for patients. The Information on Precautions, etc. should include the precautionary statement that standard treatment and follow-up, including pharmacological therapy, should be performed before using CureApp HT App. PMDA instructed the applicant to include such statement in the Information on Precautions, etc. The applicant responded as instructed.

On the basis of the above review, PMDA concluded that patients with Grade III hypertension can be included in the target patient populations because (i) CureApp HT App is expected to provide some antihypertensive effect, although the magnitude of its clinically significant add-on effect is unknown, and (ii) the risk of CureApp HT App is acceptable.

6.B.(3).2) Elderly patients

The HERB trial excluded patients aged ≥65 years with hypertension according to the inclusion criterion "Age of ≥20 and <65 years." PMDA asked the applicant to explain the efficacy and safety of CureApp HT App in this patient population.

The applicant's explanation:

The Guidelines for the Management of Hypertension describe the effectiveness of lifestyle modifications in elderly patients. [redacted]. CureApp HT App is, therefore, expected to be effective in patients aged ≥65 years with hypertension.

Dehydration due to excessive salt reduction or undernutrition due to a drastic change in seasoning are possible risks associated with hypertension treatment in elderly patients with hypertension. However, CureApp HT App [redacted]. Thus, the use of CureApp HT App does not necessarily result in excessive diet control. Exercise is associated with certain risks in elderly patients. However, CureApp HT App is designed not to suggest excessive exercise to such patients. Specifically, CureApp HT App advises patients with increased arthropathy or risks related to cardiac load to consult with their physicians and not to exercise when they have dehydration, physical deconditioning, shortness of breath, lightheadedness, or other physical problems.

In the HERB trial, as shown in Figure 16, [redacted].

Elderly patients will select lifestyle habits by themselves according to their preference and try to modify them. CureApp HT App is also expected to have a higher antihypertensive effect than the standard treatment in elderly patients with hypertension, as seen in the HERB trial. The risks of CureApp HT App, therefore, appear to be acceptable.

Figure 16.

PMDA's view:

The Guidelines for the Management of Hypertension explains the significance of lifestyle modifications in elderly patients. However, this fact alone does not prove that CureApp HT App can provide a clinically significant add-on effect in elderly patients compared with the standard treatment. There is a concern that elderly patients may not fully understand advice presented on the patient app because of deterioration of cognitive function. This may reduce the efficacy or lead to misinterpretation of advice that is intended to help patients reduce risks. However, lifestyle modifications are also recommended to elderly patients with hypertension. The use of CureApp HT App in combination with the standard treatment according to the Guidelines for the Management of Hypertension is likely to enhance the antihypertensive effect of the standard treatment to some extent by aiding patients in modifying their lifestyle habits. Patients with cognitive impairment may be unable to use CureApp HT App properly or to reduce risks associated with the use of CureApp HT App sufficiently. PMDA instructed the applicant to provide precautions about the use of CureApp HT App in elderly patients with cognitive impairment in the Information on Precautions, etc. The applicant responded as instructed.

On the basis of the above review, PMDA concluded that elderly patients with hypertension can be included in the target patient populations because CureApp HT App is expected to produce some antihypertensive effect provided that precautions for use in patients with reduced cognitive function are appropriately communicated to healthcare professionals, although whether it has a clinically significant add-on effect is unknown.

6.B.(3).3) Pediatric patients

The HERB trial excluded patients aged <20 years with hypertension. In contrast, the applicant selected the age of 7 years as the lower age limit of the target patient population. PMDA asked the applicant to explain the efficacy and safety of CureApp HT App in pediatric patients.

The applicant's explanation:
According to the Guidelines for the Management of Hypertension, lifestyle modifications are effective in pediatric patients as well. The mechanism of action of CureApp HT App is based on lifestyle modifications. The results of the HERB trial indicate that this concept has been achieved. CureApp HT App is, therefore, expected to be effective in patients aged <20 years with hypertension. The treatment of pediatric hypertension requires different considerations from those in the treatment of adult hypertension, including the necessity of support in dietary therapy, the intensity of exercise therapy, and the method of blood pressure measurement. Since content (e.g., message) displayed on the patient app of CureApp HT App is not adjusted for pediatric use, the considerations shown below are required.

Pediatric patients must use CureApp HT App with an aid by their caregivers for dietary therapy, and this should be communicated to users. The content about exercise therapy and the method and frequency of blood pressure measurement suggested by CureApp HT App differ from those recommended by the Guidelines for the Management of Hypertension. Users should be informed of the appropriate methods.

As shown in Figure 16, subjects themselves selected lifestyle habits to be changed according to their preference in the HERB trial. CureApp HT App is, therefore, expected to produce a higher antihypertensive effect than the standard treatment in pediatric patients with hypertension, as seen in the clinical trial.

PMDA's view:
The guidelines for diagnosis and treatment of pediatric patients with hypertension, including diagnostic criteria for hypertension and target salt intake substantially differ from those for adult patients. CureApp HT App is designed for use in adults, and its efficacy in pediatric patients is unknown because CureApp HT App has inadequate content about lifestyle modifications in children, such as unnecessary approaches to smoking cessation or drinking and stress management intended for adults. For these reasons, PMDA asked the applicant to re-discuss the appropriate age range for the use of CureApp HT App.

The applicant responded that they planned to limit the use of CureApp HT App to adults and include the lowest age limit of the target patient populations in the Intended Use section.

PMDA concluded that there was no particular problem with the applicant's response.

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 efficacy of CureApp HT App was evaluated in a clinical trial conducted in an environment close to routine clinical practice. The clinical trial, which enrolled a sufficient number of patients in Japan, showed the clinical effectiveness of CureApp HT App. The clinical trial conducted in an environment

close to routine clinical practice revealed no CureApp HT App-associated adverse event that might raise a safety concern. In addition, CureApp HT App is highly safe by nature. There is no particular safety concern about the use of CureApp HT App.

On the basis of the above review, no use-results survey of CureApp HT App is required.

7.B Outline of the review conducted by PMDA

The applicant's explanation is acceptable. There appears to be no substantial safety concern associated with the use of CureApp HT App in the post-marketing setting, because (i) an adequate risk management system has been introduced to avoid the use in the patient populations that were excluded from the HERB trial, (ii) the patient app is locked if patients do not receive a medical consultation from their treating physicians for an extended period of time, and (iii) patients are allowed to use CureApp HT App only under the supervision of their treating physicians. On the basis of the above review as well as the conclusion of the Expert Discussion, PMDA concluded that CureApp HT 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 and a use-results survey of CureApp HT App, therefore, had little necessity.

8. Documents Relating to Information for Precautions, etc. Specified in Paragraph 1 of Article 63-2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, in Relation to Notification Pursuant to the Same Paragraph of the Act

8.A Summary of the data submitted

The applicant submitted Information on Precautions, etc. (draft) as attachment in accordance with the Notification titled "Application for Marketing Approval of Medical Device" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, as described earlier in Section "6.B Outline of the review conducted by PMDA," PMDA concluded that there was no particular problem with the proposed Information on Precautions, etc., provided that the applicant would advise necessary precautions.

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 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

CureApp HT App is a digital therapeutic software program for patients with essential hypertension. The key issues in the review of CureApp HT App were (1) the clinical positioning of CureApp HT App, (2) the efficacy and safety of CureApp HT App, (3) the target patient population of CureApp HT App, and (4) measure to maintain the efficacy of CureApp HT App. PMDA's view based on the comments from the Expert Discussion are described in the sections below.

(1) Clinical positioning of CureApp HT App

The HERB trial demonstrated that CureApp HT App had a higher antihypertensive effect than the standard treatment alone in patients with essential hypertension requiring advice on lifestyle modifications. In the management of hypertension, CureApp HT App alone cannot be used for treatment but it is used in combination with the recommended conventional standard treatment. CureApp HT App should be positioned as an add-on to the standard treatment, which must be clearly stated in the Intended Use section.

(2) Efficacy and safety of CureApp HT App

The HERB trial showed a higher antihypertensive effect in the intervention group than in the control group. The trial also showed that the proportion of patients who successfully managed hypertension tended to be higher in the intervention group than in the control group. These results suggest that CureApp HT App is expected to help patients make and maintain lifestyle modifications. The effect of CureApp HT App is dependent on [redacted]. CureApp HT App is intended to be used as an aid to help patients modify their lifestyle habits under the supervision of their treating physicians after the patients are fully informed of its use. The patient app is locked if patients do not receive a medical consultation from their treating physician for an extended period of time. For these reasons, CureApp HT App is unlikely to pose any particular risk to patients. On the basis of the above and taking the risk of CureApp HT App into consideration, the clinical usefulness of CureApp HT App has been shown.

(3) Intended population of CureApp HT App

Of the target patient populations for CureApp HT App initially proposed by the applicant, patients with Grade III hypertension, elderly patients, and pediatric patients were not enrolled in the HERB trial.

Patients with Grade III hypertension and elderly patients receive advice on lifestyle modifications similarly to the patient populations included in the HERB trial. The use of CureApp HT App is expected to enhance the antihypertensive effect of the standard treatment by aiding physicians in giving guidance on lifestyle modifications. Strenuous exercise, or a delay in or deviation from standard treatment, including pharmacological therapy, may pose a health risk to patients with Grade III hypertension. This patient population is given necessary precautions after they are examined for cerebro-cardiovascular risk factors, cerebro-cardiovascular complications, etc. as done in the current hypertension management. The risk associated with strenuous exercise is acceptable as long as patients are able to interpret relevant messages displayed on the patient app. To reduce the risk of a delay in or deviation from standard treatment, the Information on Precautions, etc. should include the precautionary statement that standard treatment and follow-up, including necessary pharmacological

therapy, should be performed before starting treatment with CureApp HT App. Elderly patients may be unable to use CureApp HT App properly because of their impaired cognitive function. A warning about this risk should be included in the Information on Precautions, etc.

The efficacy of CureApp HT App in pediatric patients remains unknown because (i) the diagnostic criteria and treatment policy for hypertension differ between pediatric patients and adult patients, and (ii) CureApp HT App is not designed to be used in pediatric patients.

Based on the above, patients with Grade III hypertension and elderly patients can be included in the target patient populations of CureApp HT App, but pediatric patients should not.

(4) Measure to maintain efficacy

The patient app of CureApp HT App provides patients with knowledge about hypertension treatment. This app is also intended to encourage patients to make lifestyle modifications that may contribute to lowering blood pressure and to keep these new habits. How patients, who are users of the patient app, understand content on the app and change their lifestyle behaviors contributes to the efficacy of CureApp HT App. Such characteristics of CureApp HT App preclude identifying factors influencing users' behavioral change. The magnitude of the impact of a change in message content on the efficacy and safety of the treatment cannot be assessed without clinical evaluation.

In addition, when content presented by CureApp HT App becomes outdated as time goes by or people's lifestyle changes because of external factors, such as a pandemic of an infectious disease, guidance by the patient app may not lead to a similar behavior change to that achieved in the clinical trial, possibly resulting in the reduced efficacy of CureApp HT App. In order to maintain the efficacy of CureApp HT App, therefore, it is critical to update message content, interface, and other features of the patient app in a timely manner so that they match the times and lifestyle.

Considering the indication and clinical positioning of CureApp HT App, as well as its mechanism of action that is expected to [redacted], the risk associated with the use of CureApp HT App in patients is negligible. Any change in the target patient populations, clinical positioning, and [redacted] of the patient app will not pose any unacceptable risk to patients as long as it is ensured that CureApp HT App is used under the supervision of physicians. It is rather important to update the interference and other features in accordance with the times in order to maintain the clinical efficacy of CureApp HT App.

The following approval condition is imposed for CureApp HT App to be approved. The applicant is required to submit an annual report.

Approval Condition

The applicant is required to collect post-marketing information on the efficacy of the product annually after approval and to report it to the Pharmaceuticals and Medical Devices Agency to verify that the efficacy of the product is maintained.

To assess the maintained efficacy of CureApp HT App, the applicant should collect blood pressure measurement data (a patient outcome) and confirm whether patients have used CureApp HT App continuously. The applicant must include this information in annual reports (Instructions).

As a result of the above review, PMDA has concluded that CureApp HT App may be approved for the intended use shown below.

Intended Use
Adjunctive treatment of essential hypertension in adults

Approval Condition
The applicant is required to collect post-marketing information on the efficacy of the product annually after approval and to report it to the Pharmaceuticals and Medical Devices Agency to verify that the efficacy of the product is maintained.

The product is not classified as a biological product or a specified biological product. No use-results survey of CureApp HT App is required.

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

Instructions
The applicant is required to submit annual reports to report data on user’s blood pressure, the usage rate of CureApp HT App, and its post-marketing efficacy. The applicant is also required to take adequate management measures to assure the integrity of these data.

References

[1] The Japan Society of Hypertension. Guidelines for the Management of Hypertension 2019. 2019

[2] Nakano M, Eguchi K, Sato T, et al. Effect of Intensive Salt-Restriction Education on Clinic, Home, and Ambulatory Blood Pressure Levels in Treated Hypertensive Patients During a 3-Month Education Period. *J Clin Hypertens (Greenwich).* 2016;18(5):385-92.

[3] Ohta Y, Tsuchihashi T, Ueno M, et al. Relationship between the Awareness of Salt Restriction and the Actual Salt Intake in Hypertensive Patients. *Hypertens Res*. 2004;27(4):243-6.

[4] Ohta Y, Tsuchihashi T, Onaka U, et al. Long-Term Compliance with Salt Restriction in Japanese Hypertensive Patients. *Hypertens Res.* 2005;28(12):953-7.

[5] Whelton PK, Carey RM, Aronow WS, et al.
2017 CC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018;138(17):e484-e594.

[6] Kario K. Differential Approaches are Much Needed for “Real World” Management of Hypertension in the Era of “Hypertension Paradox”. *Curr Hypertens Rev*. 2018;14(1):2-5.

[7] Working group’s report on review of the calculation methods, etc. for “Average interval between hospital visits” and “Total number of patients” in patients survey (in Japanese). August 2021.

[8] Satoh M, Maeda T, Hoshide S, et al. Is antihypertensive treatment based on home blood pressure recommended rather than that based on office blood pressure in adults with essential hypertension? (meta-analysis). *Hypertens Res*. 2019;42(6):807-816.

[9] Li Y, Wei FF, Thijs L, et al. International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes Investigators. Ambulatory hypertension subtypes and 24-hour systolic and diastolic blood pressure as distinct outcome predictors in 8341 untreated people recruited from 12 populations. *Circulation.* 2014;130:466-74.

[10] Ettehad D, Emdin A.C, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet.* 2016;387:957-967.