Clinical Trial Protocol Number：YCU - 21001
Ver1.1
Date Created：August 19th, 2021

Informed Consent Form

Phase II physician-initiated clinical trial investigating the efficacy and safety of guanabenz acetate for non-alcoholic fatty liver disease associated with hypertension
(G-Flash study)

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1. Introduction

I will now explain to you about the clinical trial for your drug candidate, WY-8678 (guanabenz acetate). Please decide whether or not to participate in this clinical trial after fully understanding the contents of the explanation. You may take this explanation home with you and discuss it with your family members before making a decision. This is not mandatory. You are free to decide whether or not to participate in this clinical trial. Even after you have agreed to participate in the clinical trial, you may stop at any time, regardless of the reason. You will not be treated unfavorably or lose any medical benefits if you do not participate in the clinical trial, withdraw your consent during the clinical trial, or discontinue the clinical trial midstream.
If you have any questions or concerns, or need further explanation, please do not hesitate to ask your physician.

2. What is a Clinical Trial

In order for a new medication to be used by patients, its efficacy (effectiveness) and undesirable effects (side effects), etc., must be confirmed by the Ministry of Health, Labor and Welfare. To do this, we first look for ″drug candidate″ ingredients as shown in Figure 1-1 (Step 1). Then, we confirm in animals or other animals how the ingredient works (Step 2). Next, after confirming the safety of the drug in healthy volunteers, we investigate the ″effects″ and ″side effects″ of the drug in patients (Step 3). This type of study to investigate the drug as a drug is called a ″clinical trial″ (Chiken).

(Chiken). The drug candidate used in the study is called an ″investigational new drug. Clinical trials are conducted in consideration of the human rights and safety of the participants. The clinical trial is conducted in accordance with the ″Good Clinical Practice (GCP) for Drug Trials″ established by the Japanese government, taking into consideration the human rights and safety of

the participants. The results of the clinical trial, in which many patients cooperate, are compiled and finally reviewed by the government (Ministry of Health, Labour and Welfare) for approval as a new ″medicine″ (Step 4), and if approved, the drug will be used in the world (Step 5). If the drug is approved, it can be used in the market (Step 5). All the medicines we use today have had their efficacy and side effects confirmed through clinical trials.

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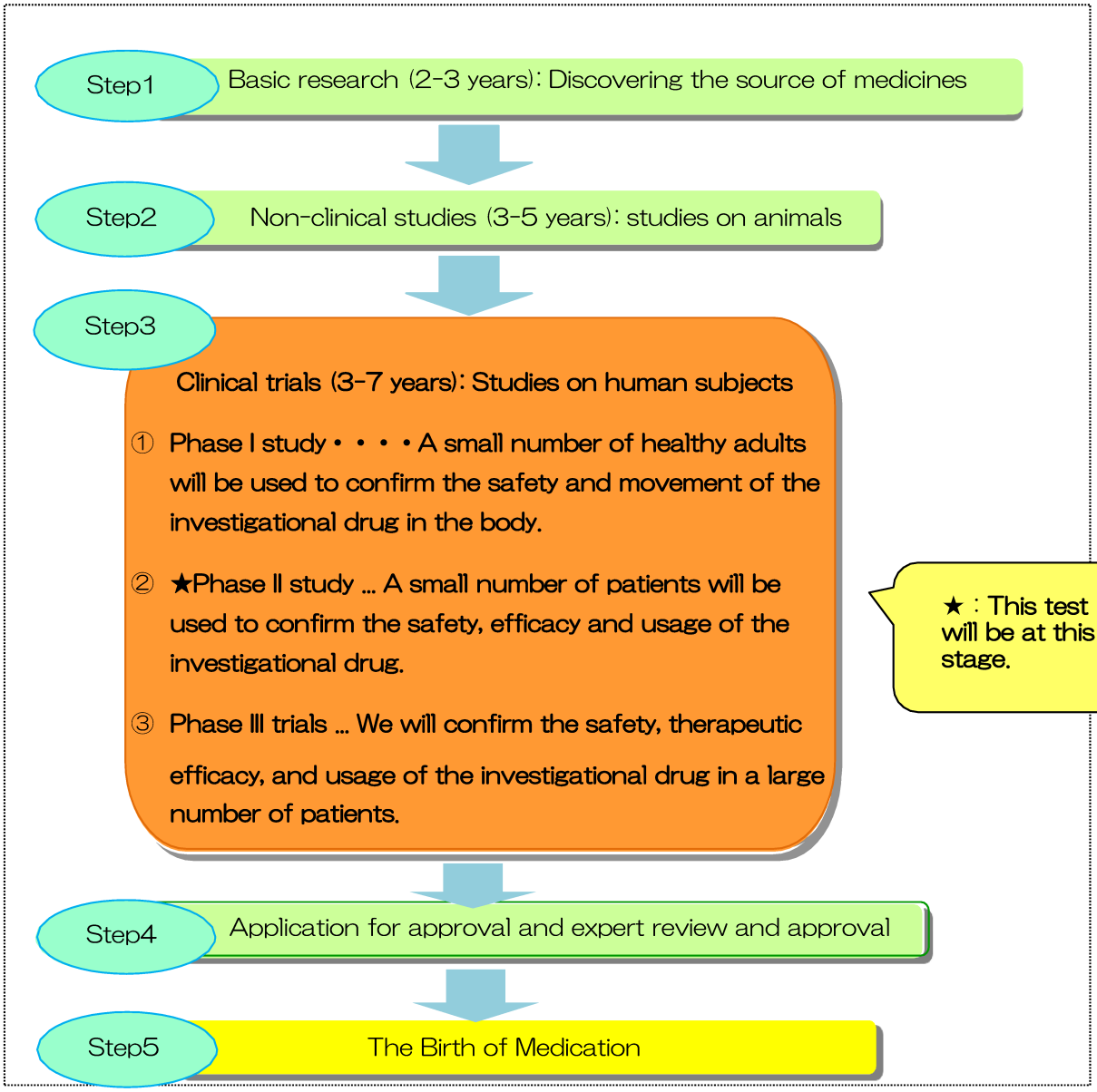
Figure 1-1 Flow chart of how a new drug is created



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In addition, clinical trials include the research aspect of obtaining new and unknown information as well as the objective of obtaining information necessary for drug review. Therefore, clinical trials are conducted in compliance with the strict rules and standards set by the government, and the content of the clinical trial plan is thoroughly reviewed and approved by the Clinical Trial Review Committee to ensure that it is scientifically and ethically valid and that there are no problems with its implementation. In addition, please understand in advance if you wish to participate in the clinical trial that the number of hospital visits and examinations may increase from usual.

About the Clinical Trial Review Committee

Our hospital has a Clinical Trial Review Committee established by the hospital director, which includes physicians, non-physicians, and members of the public outside the hospital. This committee reviews and approves clinical trials to ensure that there are no scientific or ethical problems, and that the physicians involved in the trials are qualified. The committee also reviews whether the continuation of the clinical trial is appropriate.

The Clinical Trial Review Committee's procedure manual and review details can be found on the website below or at the Clinical Trial Management Office. For more information, please do not hesitate to contact your physician or the consultation desk.

< Our Clinical Trial Review Committee>

Establisher: Yokohama City University Hospital Hospital Director
Name: Clinical Trial Review Committee of Yokohama City University Hospital Type: Clinical Trial Review Committee of the Implementing Medical Institution
Location: 3-9 Fukuura, Kanazawa-ku, Yokohama City, Kanagawa Prefecture Website address: http://www-user.yokohamacu.ac.jp/~ynext/trial/irb/

3. About Your Disease

Your disease is called non-alcoholic fatty liver disease (shibokan shikan), a disease in which fat accumulates in the liver even though you do not drink much alcohol and may be caused by overeating, being overweight, or lack of exercise. (This type is not caused by excessive alcohol consumption.) These are divided into two types: ″nonalcoholic fatty liver,″ which progresses slowly, and ″nonalcoholic steatohepatitis,″ in which inflammation is added to nonalcoholic fatty liver, which progresses quickly, and some people may develop cirrhosis or even liver cancer if the disease gets worse.

4. About the investigational drug

WY- 8678 (guanabenz acetate), the investigational drug that will be used if you agree to participate in this clinical trial, has been approved for the treatment of essential hypertension since 1985. This investigational drug is believed to improve fatty liver by improving insulin resistance. Insulin resistance is a condition in which insulin, which controls blood sugar, does not work sufficiently due to obesity. It is expected to improve obesity, diabetes, and other conditions said to be related to nonalcoholic fatty liver disease.
The investigational drug in this study is a medication containing the active ingredient of guanabenz acetate.

5. Purpose of the Clinical Trial

The purpose of this clinical trial is to investigate the safety and efficacy of the investigational drug in patients with nonalcoholic fatty liver disease/nonalcoholic steatohepatitis complicated with hypertension by taking the investigational drug twice a day.

Specifically, the investigational drug containing 2 mg of guanabenz acetate will be evaluated when the patients take ″1 tablet twice a day″ and when they take ″2 tablets twice a day″. The efficacy and safety of the investigational drug containing 2 mg of guanabenz acetate will be studied when taken twice daily.

For details of the dosage method, please refer to ″(3) Usage of the investigational drug″ in ″6. Methods of the clinical trial″.

This clinical trial will be conducted only at our hospital, and approximately 28 people are expected to participate.

This clinical trial is being conducted with the support of Asuka Pharmaceuticals, Inc. for the costs related to its operation. However, we will not change your treatment policy or compromise the fairness of the clinical trial by giving priority to the interests of ASKA Pharmaceuticals Co.

6. Methods of the clinical trial

Conditions for Participation in Clinical Trials

（1） Criteria for participation in the clinical trial

To ensure the safety of the clinical trial, the following conditions must be met in order to participate in this clinical trial. You will be asked to undergo several other tests, and the physician in charge will decide whether or not you can participate in the clinical trial. Depending on the results, you may not be able to participate in the clinical trial.

1）Who can participate

- Patients between 20 and 75 years of age at the time of consent
- Patients who have given written consent in person

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- Patients who have been diagnosed with essential hypertension and whose blood pressure at screening is 130 mmHg or higher systolic and/or 85 mmHg or higher diastolic.
- Patients diagnosed with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis
- Liver fat content of more than 8% on MRI-PDFF at screening
- MR elastography value less than 3.6 kPa at screening
- BMI greater than 25 kg/m2 at screening
- Patients who have been on diet and exercise therapy for 12 weeks prior to screening with no improvement
- Willingness to maintain a stable diet and physical activity throughout the study period

2) Who cannot participate?

- Pregnant, lactating, or possibly currently pregnant, or who do not agree to use contraception while participating in the clinical trial
- Have taken guanabenz acetate within 16 weeks prior to screening or have participated in other clinical studies (excluding observational studies)
- Have a drug allergy to guanabenz acetate
-
- Patients with hepatic insufficiency or cirrhosis
- Patients with the following laboratory findings ::

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1) ALT＞430 IU/L（males）ALT＞240 IU/L（females）or AST ＞300IU/L

2) PT-INR（prothrombin time - international normalized ratio）≧1.5 （excluding anticoagulation therapy）

3) Total bilirubin level > 2.0 mg/dl (except for confirmed diagnosis of Gilbert's syndrome)

4) Platelet count＜80,000／μL

5) eGFR＜45

- Patients with a history of acute or chronic liver disease or complications other than nonalcoholic fatty liver disease/nonalcoholic steatohepatitis

- Patients with a history of HIV infection

- Patients with symptoms of portal hypertension (complications: ascites, hepatic encephalopathy, varices, splenomegaly)

- Patients with a history of use of drugs related to non-alcoholic fatty liver disease or other hepatotoxins for more than 4 weeks in the year prior to screening以下の薬剤の使用がある方

1) Use of insulin, GLP-1 agonists, SGLT2 inhibitors, or thiazolidinediones in the 12 weeks prior to screening

2) Use of ursodeoxycholic acid or vitamin E in the 12 weeks prior to screening

3) Dose modification of dyslipidemia or hypertension medications in the 12 weeks prior to screening

4) Patients who have undergone dose modification of oral

diabetes medications (DPP-4 inhibitors, SU preparations, alpha-glucosidase inhibitors, metformin) in the 12 weeks prior to screening

5) Use of drugs known to have a significant effect on body weight (including over-the-counter drugs for weight loss) in the 12 weeks prior to screening

- Central nervous system depressants (barbital, thiopental sodium, morphine salt hydrate, flotillas, thiopental sodium, morphine hydrate, flotizolam, diazepam, etc.)
- Patients with a weight change of 10% in the 24 weeks prior to screening
- Patients who have undergone bariatric surgery or are scheduled to undergo surgery during the study period
- Patients with a history of type 1 diabetes mellitus
- Hemoglobin A1c (HbA1c) > 9.5% at screening or have poorly controlled type 2 diabetes mellitus
- Complicated hyperthyroidism or hypothyroidism, or those with screening results indicating thyroid dysfunction Except for those who received thyroid replacement therapy for hypothyroidism in the 12 weeks prior to screening and have stable laboratory values
- History of New York Heart Association class III or IV heart failure due to factors other than hypertension or IV heart failure due to factors other than hypertension
- History of myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke or

major surgical procedure in the 24 weeks prior to screening

- Patients with a history of drug abuse
- Patients with a malignant complication, except for those who have undergone radical surgery, completed chemotherapy/radiotherapy, or are undergoing hormone therapy.
- Patients already known to be intolerant to MRI examinations, or those for whom MRI examinations are contraindicated.
- Other patients whom the investigators deem inappropriate to conduct this clinical trial.

（2） Duration of Clinical Trial Participation

If you participate in this clinical trial, your participation period will consist of a screening period of up to 8 weeks, an investigational drug taking period of 16 weeks, and a follow-up period of 4 weeks, for a total of 28 weeks (maximum of approximately 7 months). If you decide to discontinue during the investigational drug taking period, you will still participate in the follow-up period (4 weeks after discontinuation) in principle.

（3） Usage of the investigational drug

If you are confirmed to meet the ″(1) Criteria for Participation in the Clinical Trial″ prior to the start of the clinical trial, you will be placed in one of the following dosing groups and will take the investigational drug for 16 weeks. You will be randomly assigned to one of the following groups in a 1:1 ratio according to a predetermined method, and neither you nor your physician will be able to choose which group you will be placed in. This is to remove any preconceived notions and to properly evaluate the efficacy and safety of the investigational drug.

【Dosage of the investigational drug】

Group 1	Study drug containing 2 mg of guanabenz acetate 1 tablet twice a day (2 tablets/day)
Group 2	Study drug containing 2 mg of guanabenz acetate 2 tablets twice daily (2 tablets per day)

• The investigational drug will be started after dinner on the first day of administration and will be taken until after breakfast on the day of the visit 16 weeks later.

• The investigational drug will be taken twice a day after breakfast and dinner. Guanabenz acetate should be taken one or two

tablets at a time.

• If you miss a dose, please take it at least 6 hours before the next dose.

• Store investigational drugs away from high temperatures and moisture.

（4） Schedule

After you give your consent to participate in this clinical trial, the examinations and observations listed in Table 6-1 will be performed according to the schedule. In addition, changes in physical condition or physician's orders may require visits other than those stipulated, additional tests may be required, or the amount of blood drawn may increase or decrease. The specific schedule is as follows

1）Screening

If you agree to participate in this clinical trial, you will undergo a screening to confirm that your current physical condition meets the criteria for participation in this clinical trial.

2）Treatment period

Patients who have been screened and found to be safe to participate in this clinical trial will be given the investigational drug. During the period of taking the investigational drug, we will conduct predetermined tests and observe the patient's physical condition and the progress of the disease to determine whether the patient can continue in the clinical trial.

3）Follow-up

Four weeks after completion of the study drug, the patient will continue to receive medical examinations and tests to check the patient's condition

4）Discontinuation

If the investigational drug is discontinued during the study period, the patient will undergo a medical examination and tests at the time of discontinuation. In addition, as a general rule, patients will be asked to come back to the clinic 4 weeks after the discontinuation visit to have a medical examination and tests.

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Table 6-1 Clinical Trial Schedule

	Consent acquisition	Screening	Treatment period						Follow-up
		V1	V2	V3	V4	V5	V6	V7／EOT	V8
Week		Within 8 weeks prior to registration	Prior to start of administration	2 weeks	4 weeks	8 weeks	12 weeks	16 weeks	4 weeks after end of administration
Tolerable range		-8 weeks	-	±3 days	±7 days	±7 days	±7 days	±7 days	±7 days
Consent acquisition	○								
Selection criteria		○	○						
Subject background		○							
Serological test [a]		○							
Chest X-ray		○							
electro-cardiogram		○							
Physical examination [b]		○	○					○	
Vital signs c		○	○	○	○	○	○	○	○
Subjective and objective symptoms			○	○	○	○	○	○	○
Pregnancy test [d]			○					○	
MRI[e]		○						○	
Liver biopsy		△							
Randomization			○						
Hematology test / urine test [f]		○	○[j]					○	○
Endocrinological examination		○							
Biochemical test 1		○	○[j]		○	○	○	○	○
Biochemical test 2[g]		○	○[j]					○	
Other [h]			○					○	
Somatic cell genetic test			●						
Providing drugs			○		○	○	○		
Checking the medication status				○	○	○	○	○	
Survey of combination drugs		○	○	○	○	○	○	○	
Investigation of adverse events				○	○	○	○	○	○

1) Height will be measured only at screening.

2) Only applicable female patients will have a urine pregnancy test performed prior to enrollment and at 16 weeks/discontinuation.

3) Liver biopsy results (within 32 weeks prior to screening) will be collected if available.

4) Blood volume: The maximum volume of blood to be collected is approximately 45 mL at one time, and approximately 140 mL of blood will be collected for the entire trial.

5) The collected blood samples will be stored for a maximum of 5 years, after which they will be disposed of in an appropriate manner. If the blood samples and the information obtained in this study are to be used in a newly planned research study for a purpose other than this clinical trial, we will do so only after obtaining approval from an ethics review committee, etc., which will deliberate the conduct of the research from an independent and fair perspective. In such cases, we will obtain your consent again before using the information.

6) MRI will be performed to measure MR elastography and MRI-PDFF; if the study is discontinued before 16 weeks, MRI will be performed at the end of treatment if you have completed at least 4 weeks of treatment.

7) Somatic cell genetic testing will be mandatory.

*If data is available within 1 month, it will be substituted and no new test will be performed.

（5） Somatic cell gene test

The somatic cell gene test will examine the types of genes, PNPLA3 and TM6SF2, which are known to be associated with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. These genes are not inherited by offspring due to genetic changes that occur at various stages of life. It is also thought to affect non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, but since it has not been established as a diagnostic tool for the disease, the results of this test will not be shared with you.This test is mandatory for participation in this clinical trial and will require the collection of approximately 5 mL of blood. The blood sample will be stored for up to 5 years and then disposed of in an appropriate manner. If the blood samples and information obtained in this study are to be used in a newly planned research study for a purpose other than this clinical trial, it will be done only after approval is obtained from an ethics review committee that deliberates on the conduct of the research from an independent and fair standpoint. In such cases, we will obtain your consent again before using the information.

7. Expected effects and side effects

＊Expected effects

It is expected to improve non-alcoholic fatty liver disease by improving the inadequate insulin action secreted by the pancreas.

＊Expected inconvenience

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In this clinical trial, patients will be assigned to either one or two doses of the investigational drug containing 2 mg of guanabenz acetate per dose, but not all patients in either group may benefit. In addition, clinical trials may require a greater number of office visits and tests than in the general population, and the medical examinations may take longer. There are other medications and treatments that should not be used while participating in a clinical trial. If you wish to use any of the medications or treatments listed below while participating in a clinical trial, please consult your physician in advance.

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【Medications that should not be used during the clinical trial】

Drugs	Period
(1) Ursodeoxycholic acid	From the time consent is obtained to the end of the treatment period
(2) Guanabenz analogs (clonidine, methyldopa)	
(3) Thiazolidine, glucagon-like peptide-1 (GLP-1) receptor agonist, SGLT2 inhibitor, insulin	
(4) Central nervous system depressants (barbital, sodium thiopental, morphine hydrochloride hydrate, brotizolam, diazepam)	
(5) Vitamin E	
(6) NAFLD-related drugs (amiodarone, methotrexate, systemic glucocorticoids, tetracycline, tamoxifen, higher doses of estrogen, anabolic steroids, or valproic acid than used for hormone replacement) or other hepatotoxins	
(7) Drugs that significantly affect body weight (including over-the-counter weight loss drugs)	

【From the time of screening to the follow-up end, the following therapies are prohibited:】

Therapy	Period
(1) Obesity surgery (sleeve gastrectomy, gastric bypass surgery, sleeve bypass surgery, etc.)	From the time of screening to the end of follow-up

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【Drugs restricted for concomitant use include】

Drugs	Period
(1) Antihypertensive drug	During the treatment period
(2) Drugs to treat dyslipidemia	
(3) Drugs to treat diabetes treatment (DPP-4 inhibitor, SU preparation, α-glucosidase inhibitor, metformin)	

＊About Side Effects

Guanabenz acetate is already marketed in Japan as a medication to improve essential hypertension, and the following side effects have been reported so far. Therefore, similar side effects may occur.

Not all of these side effects will occur in all patients. On the other hand, there is a possibility that unexpected side effects other than those listed here may occur, and it cannot be denied that some side effects may be serious and life-threatening.

Safety information on guanabenz acetate (product name: Wytens Tablets 2 mg) marketed in JapanSafety information of guanabenz acetate (product name: Wytens Tablets 2 mg) marketed in Japan. In 822 out of 15,358 cases (5.4%) investigated at the time of reexamination of guanabenz acetate by the Japanese Ministry of Health, Labour and Welfare (MHLW), adverse reactions were observed. The most common adverse reactions were gastrointestinal symptoms such as dry mouth (2.9%), neuropsychiatric symptoms such as drowsiness and dizziness (2.8%), and hypersensitivity symptoms such as rash (0.2%). There were no serious adverse reactions, but other adverse reactions that occurred were as follows by frequency. Please inform your doctor immediately if you experience any change in your physical condition or any symptoms that concern you in the slightest.

Appropriate treatment will be given. During the clinical trial, periodic examinations and consultations will be conducted to check for such undesirable symptoms. Unpredictable side effects may occur in addition to those listed here. Please ask your physician for the most up-to-date information regarding side effects at any time.

	0.1 ～0.5%	Less than 0.1%
Hypersensitivity	Rash	Facial eczema, urticaria, pruritus
Liver	—	AST (GOT), ALT (GPT) elevation ALT (GPT) increase
Neuropsychiatric systems	Drowsiness, dizziness, lightheadedness, dizziness, dizziness, fatigue, weakness, headache/overhead	Tinnitus, insomnia, depression, tremor
Circulatory System	—	palpitations, chest pain, bradycardia, arrhythmia, excessive hypotension
Digestive Organs	Dry mouth, abdominal discomfort, nausea	anorexia, diarrhea, constipation, vomiting, heartburn, bitter taste, stomach pain
Other	—	stiff shoulders, back pain, myalgia, numbness, cold extremities, nasal obstruction, dyspnea, facial flushing, edema, bladder tenesmus, urinary frequency Bladder tenesmus, Frequent urination

8. What to do when new information regarding the clinical trial is obtained

If there are any changes to the plan or other aspects of this clinical trial, we will explain those changes to you. If we obtain any information that may affect your willingness to participate in the clinical trial, such as information on new side effects obtained during your participation in the clinical trial, we will promptly inform you of the details of such information. At that time, we will ask you again if you are willing to continue to participate in this clinical trial. However, as described in ″9. Discontinuation of the clinical trial,″ you may withdraw from the clinical trial at any time, as your participation in the clinical trial is of your own free will.

9. Discontinuation of the clinical trial

Even after you have participated in this clinical trial, the trial may be terminated in the following cases.

（1） When this clinical trial is discontinued

1) When there are unavoidable ethical or medical reasons to ensure patient safety

2) If the scientific validity of the development of this drug is lost

3) If the investigator or the investigational site violates any ministerial ordinance, clinical trial plan, or various procedures that should be observed by the investigator or the investigational site, which is recognized as an obstacle to the proper conduct of the clinical trial.

4) When the investigator decides to discontinue or suspend the clinical trial

5) When the investigator is instructed by the investigational review committee to discontinue the clinical trial

（2） When your participation in a clinical trial is terminated

1） If you request discontinuation of the clinical trial

2) If the results of tests or your symptoms are found not to meet the conditions for participation in the clinical trial

3) If you take any medication that should not be used during the clinical trial period or receive any treatment that is prohibited

4) If your physical condition is so poor that it is difficult for you to continue the clinical trial

5) If the physician in charge decides that it is better to discontinue the study in any other case. If you discontinue the study after starting to take the investigational drug, please cooperate with the tests marked with a circle in the ″16 weeks/at discontinuation″ column of the schedule chart shown in Table 6-1 in ″6.

You will not be disadvantaged in any way in subsequent treatment after discontinuation of the clinical trial. Your treatment for your disease will be the most appropriate treatment for you from among the usual treatments. Please note that even if the clinical trial is terminated, we may use the results up to that point.

10. About other treatment methods

Currently, there are no drugs for nonalcoholic fatty liver disease that are covered by insurance in Japan, and the treatment method most often used is to improve lifestyle through diet and exercise therapy. This may improve obesity, diabetes, dyslipidemia, hypertension, and other conditions that underlie the disease, and may also lead to improvement of nonalcoholic fatty liver disease. If lifestyle modifications do not show sufficient benefit, the disease may be treated indirectly with medications for hypertension, dyslipidemia, and diabetes, but it is not yet clear whether these will have long-term benefits. If you do not participate in this clinical trial, or even if you stop the trial midway through, you can still consult with your

physician to choose an appropriate treatment option that is tailored to each patient's individual situation.

11. In case of adverse health effects

If you experience unusual symptoms while participating in a clinical trial, please contact your physician immediately. Appropriate care and treatment will be given immediately.

If you experience any side effects or other health problems due to your participation in this clinical trial during or after the trial is completed, your physician will provide you with the best possible treatment. You may also be entitled to compensation for such health problems. However, you may not receive compensation or your compensation may be limited if you did not follow the instructions of your physician, if your health damage was caused by your negligence or intention, or if it becomes clear that your health damage was not related to this clinical trial.

Please keep the receipt issued by the medical institution in a safe place, as it will be necessary for you to receive compensation.

For details on compensation, please refer to the attached document (″Compensation for Health Damage Caused″).

12. Reduction of costs associated with participation in a clinical trial

There is no cost for the investigational drug during this clinical trial. The investigational drug will be provided free of charge. However, you will be asked to pay the insurance portion of the cost of the tests (blood tests, MRI scans, etc.) performed at our hospital and the cost of medications other than the investigational drug.

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In order to reduce your transportation costs, we will pay 10,000 yen per visit for the clinical trial as a burden reduction fee. The maximum amount of payment is 80,000 yen depending on the number of times you visit the clinic. This will be transferred to your designated account by ″Yokohama Shiritsu Daigaku″ in a lump sum after the completion of the clinical trial period. Please read the separate document explaining the receipt of the Clinical Trial Cooperation Fee. This burden reduction fee may be declined for any reason.

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13. About personal information

In order to confirm that this clinical trial has been conducted correctly, including in cases where you withdrew your consent in the middle of the trial, the people involved in the clinical trial may inspect your medical records (e.g., medical records) related to the trial. The people involved in the clinical trial include personnel from the company commissioned by the investigator, people from the Clinical Trial Review Committee, people from the Ministry of Health, Labor and Welfare, and officials commissioned by the government to conduct the investigation. These people are required by law not to leak the contents of medical records and other records to outside parties, and information about your privacy will not be leaked outside the hospital.

The results obtained from this clinical trial will be reported to the company that is providing the costs related to the operation of this clinical trial, and may be used as part of the materials submitted to the government (Ministry of Health, Labor and Welfare). In addition, data obtained from this clinical trial may be presented in medical papers or at academic conferences. The information that will be used to identify you in the clinical trial report will not be your name, address, or other personal information, but rather an identification code that is a combination of numbers and letters. The list linking this identification code to your name and other information is maintained in the hospital and is controlled by the hospital's regulations on personal information management. However, among the personal information, information such as date of birth may be entered in the clinical trial report form for reasons such as to confirm the criteria for participation in the clinical trial, but even in this case, this information will not be leaked to the outside world or used for purposes other than this clinical trial. In handling personal information, we will give due consideration to the protection of your privacy. By signing the consent form after listening to this explanation, you agree to the access to your medical records and the use of your personal information (date of birth, etc.). By signing the consent form after listening to this explanation, you consent to the access to your medical records and the use of your personal information (date of birth, etc.)。

14. What you should follow

For your safety and to collect reliable data, please observe the following

(1) When you come to the clinic at 4, 8, 12, and 16 weeks/discontinuation, you will need to fast for 8 hours prior to the blood test. Therefore, please take the study drug at the following times.

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If you visit the clinic in the morning, please take the study drug without eating breakfast before coming to the clinic.
If you visit the clinic in the afternoon, please take the investigational drug before breakfast as usual and come to the clinic without eating lunch. If you visit the clinic in the afternoon, please take the study drug before breakfast as usual and visit the clinic without eating lunch.
(2) During your participation in the clinical trial, please maintain a stable diet and a normal lifestyle (physical activity).
(3) Please fill in the medication diary as instructed by the investigator or clinical trial coordinator to keep track of the medication you are taking and your daily condition.
(4) If you visit another hospital, please inform that physician that you are participating in a clinical trial. Also, please inform your physician or the clinical trial coordinator that you have seen another physician. With your permission, we may inquire with the physician at the other hospital about your medications and your condition.
(5) Please be sure to come to the hospital on your scheduled visit date. (If you are unable to make it, please let us know in advance.)
(6) If you are currently using any medications (including over-the-counter medicines and health foods), if you will be using any new medications after participating in the clinical trial, or if you will be receiving any new treatment in addition to the medications you are currently using, please contact your doctor in charge in advance. Medications may interact with each other, which means that they may have a negative effect on your health if used together, either by losing their effectiveness or by having a stronger effect.

(7) If you feel that something is wrong with your body, such as a different physical condition from usual (including broken bones, accidents, etc.), please contact your doctor anytime.
(8) On the day of your visit, please bring everything with you, including your medication log, extra study medication, study medication bag, and empty study medication sheets.
(9) Women of childbearing potential must use oral contraceptives, a contraceptive ring (IUD), pessary or condom, or other contraceptive methods during participation in the clinical trial. You will be asked to choose a contraceptive method that is appropriate for you in consultation with the investigator. If you believe that your contraceptive method was inadequate or if you become pregnant, please inform us immediately.
(10) Please be careful when engaging in hazardous activities such as drinking alcohol, working at high altitudes, driving a car, etc. while you are taking investigational drugs.
(11) Please inform your physician of any changes in your address, telephone number, or other contact information.

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15. Disaster Message Dial in the Event of a Large-Scale Disaster

In the event of a major disaster, we may contact you at the telephone numbers (including those of your family members) that we have confirmed in advance in order to confirm your safety. In the event that communication networks are disrupted, we ask for your cooperation in using the Disaster Message Dial (171). The Disaster Message Dial is a service set up 30 minutes after an earthquake of intensity 6 or higher on the Japanese seismic intensity scale to allow people in disaster-stricken areas to register and confirm their safety via telephone or the Internet.

Iwaki M, *et al. BMJ Open* 2022; 12:e060335. doi: 10.1136/bmjopen-2021-060335

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【How to record a message on the Disaster Message Dial ″171】

① Dial 171. Guidance will be given.

② Dial 1 (recording).

③ Dial your home phone numbe

④ You will be asked for the type of telephone (push type or dial type).

⑤ Follow the guidance and record your name and contact information.

【How to play Disaster Message Dial ″171】

① 1 Dial 171. Guidance will be given.

② Dial 2 (playback).

③ Dial the phone number of the person you wish to contact

④ You will be asked for the type of telephone.

⑥ You will be told from the new message.

【Disaster broadband message board ″web171】

① Search for Web171 and visit
https://www.web171.jp/

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16. Contact point for clinical trials

Yokohama City University Hospital

(1) Name of the investigator: Takaomi Shigurashi Name of your physician in charge:
Contact point for clinical trials: Yokohama City University Hospital
Contact point: 045-787-2800 (main number)

(2) Contact for consultation: Clinical Trial Management Office, Yokohama City University Hospital
Phone: 045-352-7 510 (Weekdays 9:00-17:0) 0)

(3) Contact on nights and holidays
Phone: 045-787-2 800 (Representative number)

*In case of emergency during nights and holidays, please contact the above and consult with the physician on duty in the Department of Gastroenterology.

Iwaki M, *et al. BMJ Open* 2022; 12:e060335. doi: 10.1136/bmjopen-2021-060335

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Attachment 1 Explanation of Terms

No.	Term	Explanation
1)	Cirrhosis	This is a disease in which the liver cells become inflamed, and when the inflammation is repaired over and over again, the liver becomes hard and loses function.
2)	Hepatic cancer	A disease in which liver cells become cancerous.
3)	Essential hypertension	This is a type of hypertension with no known cause, and accounts for about 90% of all hypertension cases. Intrinsic hypertension is a lifestyle-related disease that is related to genetic factors and environmental factors such as lifestyle. It is said to be a lifestyle-related disease.
4)	Insulin.	This hormone is essential for the efficient use of glucose. It is secreted by the pancreas.
5)	MRI-PDFF	One type of test performed using MRI to measure the amount of fat in the liver.
6)	MR Elastography	The liver is vibrated and the vibrating liver is MRI to image and measure the stiffness of the liver.
7)	BMI	Body mass index, a value indicating body mass index, which is calculated based on the relationship between weight and height.

8)	Liver failure	A condition in which the liver function is greatly reduced and is unable to fulfill its role This is a condition in which the liver becomes.

No.	Term	Explanation
9)	ALT	Abnormalities in the liver cause high blood levels, and it is one of the enzymes normally found in cells.
10)	AST	Abnormalities in the liver, heart, or muscles cause blood levels is elevated and is one of the enzymes normally present in cells.
11)	PT - INR	This test measures how long it takes for the blood to clot.
12)	Bilirubin	It is a pigment formed when red blood cells break down. It is a pigment that is formed when red blood cells break down. A type of cellular component of the blood.
13)	Platelet	A type of cellular component of blood.
14)	e GFR	It indicates how well the kidneys are able to excrete waste products into urine. The lower the value, the worse the kidney function is.
15)	HIV	The lower the value, the poorer the kidney function. A virus that infects a person's immune cells and causes acquired immunodeficiency syndrome (AIDS)

No.	Term	Explanation
16)	Ascites	The membrane that surrounds the organs in the abdomen is called the peritoneum. The peritoneum creates a space called the peritoneal cavity to reduce friction between organs. The peritoneal cavity normally contains 20 to 50 mL of water, but if a greater volume of water than usual accumulates due to various diseases, the condition is called ascites.
17)	Hepatic encephalopathy	This complication occurs when toxic substances (e.g., ammonia) that would be metabolized by the normal liver reach the brain.
18)	Vascular aneurysm	The veins in the hands and feet have valves to prevent backflow and allow blood to return to the heart. When these valves fail to work properly, causing backflow, or when large veins become clogged, the venous pressure becomes high. For these reasons, the veins near the skin become large, long, and swollen.
19)	Splenomegaly	This is a condition in which the spleen becomes swollen and enlarged.
20)	Portal hypertension	Blood flow from the intestinal tract and spleen passes through the ″portal vein″ to the portal vein″ to the liver. Portal hypertension is a condition in which the portal hypertension is a condition in which

		the blood flow in the portal vein is blocked for some reason and the blood pressure in the portal vein rises.

No.	Term	Explanation
21)	GLP-1 agonist	The drug binds to the GLP-1 receptor in the pancreas and stimulates the secretion of insulin, thereby lowering blood glucose levels. This is a drug that lowers blood glucose levels.
22)	SGLT2 inhibitor	A drug that lowers blood glucose levels by suppressing the uptake of glucose from the renal tubules and facilitating the excretion of sugar in the urine.
23)	DPP-4 inhibitor	A medication that lowers blood glucose levels by strengthening the function of the hormone incretin in the pancreas.
24)	SU preparation	Sulfonylureas. A drug that stimulates insulin secretion in the pancreas. A medication that stimulates insulin secretion in the pancreas.
25)	Alpha glucosidase inhibitor	By slowing down the digestion and absorption of sugar in the small intestine This is a drug that improves postprandial hyperglycemia by slowing down the digestion and absorption of sugar in the small intestine.
26)	CNS depressants	A drug that acts on the central nervous system and suppresses its function. They include sedatives, tranquilizers, and sleep inducers.

27)	Beta-blockers	Medications that improve hypertension, angina pectoris, heart failure, etc. by suppressing blood pressure, heart rate, etc.

No.	Term	Explanation
28)	Type 1 glycosuria Disease	Diabetes is a disease that causes blood glucose levels to rise due to poor insulin function, and is classified into several types depending on its cause. Type 1 diabetes occurs when the beta cells that make insulin in the pancreas are destroyed, resulting in a weakened ability to produce insulin or the inability to produce insulin.
29)	HbA1c (Hemoglobin A1c)	Hemoglobin, a protein in the red blood cells of the blood (Hb), a protein bound to glucose. High blood glucose levels result in a high HbA1c. The HbA1c value obtained from a blood test can be used to estimate the state of blood glucose from that day to about two months ago.
30)	Type 2 glycosuria	Blood glucose levels become high when insulin production becomes difficult (insulin hypoglycemia) or insulin becomes less effective (insulin resistance). In addition to genetic influences, there are environmental causes of type 2 diabetes, such as overeating, lack of exercise, and obesity.

No.	Term	Explanation
31)	Hyperthyroidism	This is a disease in which the thyroid gland produces too much thyroid hormone and is overactive. Common symptoms include swelling of the thyroid gland, tachycardia (rapid pulse), trembling of the fingers, sweating easily, weight loss despite eating a lot, irritability, fatigue, and occasional weakness of the limbs.
32)	Hypothyroidism	The thyroid hormone action in the blood is lower than necessary. Common symptoms of hypothyroidism include lethargy, fatigue, swelling, coldness, weight gain, slowness of movement, poor memory, and constipation.
33)	Myocardial infarction	It is a condition in which the coronary arteries become completely clogged or thinned rapidly, causing the heart muscle cells to die and lose function.
34)	Unstable angina pectoris	Angina attacks become more and more frequent. and occur not only with exertion, but also at rest.
35)	Percutaneous coronary intervention	When a narrowed coronary artery is found, the narrowed coronary artery can be catheterized. The narrowed coronary artery is widened using a catheter to

		facilitate the flow of blood.

No.	Term	Explanation
36)	Coronary artery bypass grafting	This surgery is performed for angina pectoris or myocardial infarction caused by narrowing or clogging of the coronary arteries.
37)	Stroke	This is a disease in which the brain is damaged due to clogging or rupture of blood vessels in the brain.
38)	MRI scan	An examination in which the patient is placed inside a cylinder made of powerful magnets and the organs and blood vessels of the body are photographed using the power of magnetism.
39)	Liver biopsy	It is a test in which a part of the liver is removed to diagnose the disease.
40)	Shaking of the liver	A ″tremor″ that occurs even though one does not intend to move.
41)	Bladder tenesmus	A condition in which a strong urge to urinate occurs immediately after urination.

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Attachment 2 **Compensation in the Event of Health Damage**

Phase II physician-initiated clinical trial investigating the efficacy and safety of guanabenz acetate for non-alcoholic fatty liver disease associated with hypertension
(G-Flash study)

（physician-initiated clinical trial）

Although this clinical trial will be conducted with the utmost care, we have established policies and procedures regarding compensation in the unlikely event that you suffer any adverse health effects as a result of the investigational drug or the conduct of the clinical trial.
This document is intended to explain in more detail the indemnity provisions of the Consent Explanation Document. Please keep this document together with a copy of the consent document.
If you experience any side effects or other health problems, please do not hesitate to report them to your physician, clinical trial coordinator, etc. We will take appropriate measures that we believe are best for you, including treatment.

1.compensation for any health problems that may occur during this clinical trial

(1) Principle of Compensation

1) Compensation is to appropriately compensate for the loss in the event of a health hazard to you, even if the medical institution is not legally responsible (even in the absence of

negligence), based on the purpose of the GCP ordinance (rules for conducting a clinical trial set by the government).

2) If your participation in this clinical trial results in any health problems, you will be compensated in accordance with the Compensation Policy and Procedures.

3) If you are found liable, you may file a lawsuit for damages. This compensation plan does not preclude you from exercising your right to claim damages.

(2) Compensation standards

The compensation for this clinical trial includes disability compensation and survivors' compensation in the event of residual disability (Grade 1 or 2) or death. Medical expenses and medical benefits will not be paid in this clinical trial.
Furthermore, compensation in the form of medical care will be provided for health problems other than residual disability (Grade 1 to 2) and death. Medical expenses in such cases will be paid by your health insurance, and you will be asked to bear a portion of the medical expenses.

(3) Cases not covered by the indemnity

1) If there is no causal relationship between your health damage and this clinical trial, you are not eligible for compensation.
2) If we or our investigators or other third parties are legally responsible for your health damage, you are not eligible for compensation.
3) Damage to your health caused by your willful act is not covered by the compensation.

(4) When limiting coverage

If the health problem was caused by your gross negligence (e.g., making a false or false declaration, failing to follow the dosage and administration instructions given, or not following the instructions of the investigator), the compensation payment may be reduced or you may not receive compensation.

2. Compensation procedures

(1) What to do in the event of a health hazard

If you suffer any health problems as a result of this clinical trial, we will take the necessary measures that we believe are best for you, including treatment.

(2) Offers of Compensation

If you believe that you have suffered from side effects or other health problems, please notify your physician, clinical trial coordinator, or other relevant personnel. The investigator will determine the causal relationship between the adverse health effects and the clinical trial, and will explain to you whether the adverse health effects are compensable or not.
If you have any other questions regarding compensation, please do not hesitate to contact the investigator.

3. Handling of Personal Information

In accordance with the ″Personal Information Protection Law,″ your personal information that we obtain in the course of providing compensation will be appropriately managed and taken care of, and will not be used for any purpose other than the payment of compensation.

4. Other

If you have any questions regarding compensation, please do not hesitate to contact the investigator, clinical trial coordinator, or clinical trial consultation service as indicated in the explanatory document.

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Consent form

Registration Number （___-_____） 【For medical records】

I have been informed of the details of this clinical trial (Phase II physician-initiated clinical trial investigating the efficacy and safety of guanabenz acetate for non-alcoholic fatty liver disease associated with hypertension), and I fully understand and agree to participate in this clinical trial on my own volition.

I have also received and retain a copy of the explanation document and this consent form.

Signature of the clinical trial participant

Date of agreement (YYYY/MM/DD)：_____/____/
Name：

Agree to receive burden reduction costs（ Yes • No ）

Signature of the physician who described the research

Date of explained (YYYY/MM/DD)：_____/____/
Name：

Signature of the collaborator who provided supplementary information

Date of explained (YYYY/MM/DD)：_____/____/
Name：

Date of consent received (YYYY/MM/DD)：_____/____/

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Consent form

Registration Number （ - ） 【For Clinical Trial Office】

I have been informed of the details of this clinical trial (Phase II physician-initiated clinical trial investigating the efficacy and safety of guanabenz acetate for non-alcoholic fatty liver disease associated with hypertension), and I fully understand and agree to participate in this clinical trial on my own volition.

I have also received and retain a copy of the explanation document and this consent form.

Signature of the clinical trial participant

Date of agreement (YYYY/MM/DD)： / /
Name：

Agree to receive burden reduction costs（ Yes • No ）

Signature of the physician who described the research

Date of explained (YYYY/MM/DD)： / /
Name：

Signature of the collaborator who provided supplementary information

Date of explained (YYYY/MM/DD)： / /
Name：

Date of consent received (YYYY/MM/DD)： / /

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Consent form

Registration Number （___-_____） 【For patient storage】

I have been informed of the details of this clinical trial (Phase II physician-initiated clinical trial investigating the efficacy and safety of guanabenz acetate for non-alcoholic fatty liver disease associated with hypertension), and I fully understand and agree to participate in this clinical trial on my own volition.

I have also received and retain a copy of the explanation document and this consent form.

Signature of the clinical trial participant

Date of agreement (YYYY/MM/DD)：_____/____/
Name：

Agree to receive burden reduction costs（ Yes • No ）

Signature of the physician who described the research

Date of explained (YYYY/MM/DD)：_____/____/
Name：

Signature of the collaborator who provided supplementary information

Date of explained (YYYY/MM/DD)：_____/____/
Name：

Date of consent received (YYYY/MM/DD)：_____/____/