Information Document / Consent Form

For Patients

Title of Clinical Trial: A Phase II Investigator-led Study to Compare the Efficacy and Safety of Combined Elobixibat and Cholestyramine to that of Placebo, Cholestyramine Monotherapy or Elobixibat Monotherapy for Nonalcoholic Fatty Liver Disease

Clinical Trial Protocol No.: YCU-19002
Yokohama City University Hospital Ver1.4
Date prepared: February 20, 2020

Contents

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1. Introduction

We would now like to provide you with explanations about the clinical trial on the candidate drugs AJG533 (Elobixibat) and CTM27 (Cholestyramine). Please decide whether or not you would like to participate in this study, after listening to the explanations carefully and understanding what you are being told. You may take this written information document home and discuss the participation with your family. You are not being compelled to participate. Whether or not you participate in the study is entirely up to you. Even if you agree to participate in the study, you may stop doing so at any time without giving a reason. Furthermore, please understand that you will not be mistreated or lose any healthcare benefits for refusing to participate or withdrawing your consent to participate during the study.

If you would like more explanations or have questions you wish to ask, please do not hesitate to ask the investigator.

2. What is a Clinical Trial?

In order to have patients use a new drug, the Ministry of Health, Labour and Welfare must have checked the drug for its medicinal effect (efficacy) and for its undesirable effects (side effects). The process of drug development begins with a search for a “Drug candidate” as shown in Fig. 1-1 (Step 1). This substance is then tested in animals to see what kind of an effect it has (Step 2). The safety of the substance as a drug is then checked by having healthy volunteers use it, and patients are recruited to investigate the “efficacy” and “safety” of the drug (Step 3). A study that investigates a drug in this manner is called a “Clinical Trial”. A drug candidate that is investigated in such a study is called a “Study Drug”. Clinical trials are conducted based on the “Good Clinical

Practice (GCP) Standards" outlined by the government, with respect to the human rights and safety of its participants.

The results of clinical trials conducted with the help and cooperation of many patients are then compiled so that the government (MHLW) may ultimately review the data to see whether the substance can be approved as a "Drug" (Step 4). Once approved, it is ready for common use (Step 5). All drugs that we use today have had their efficacy and safety checked through such clinical trials.

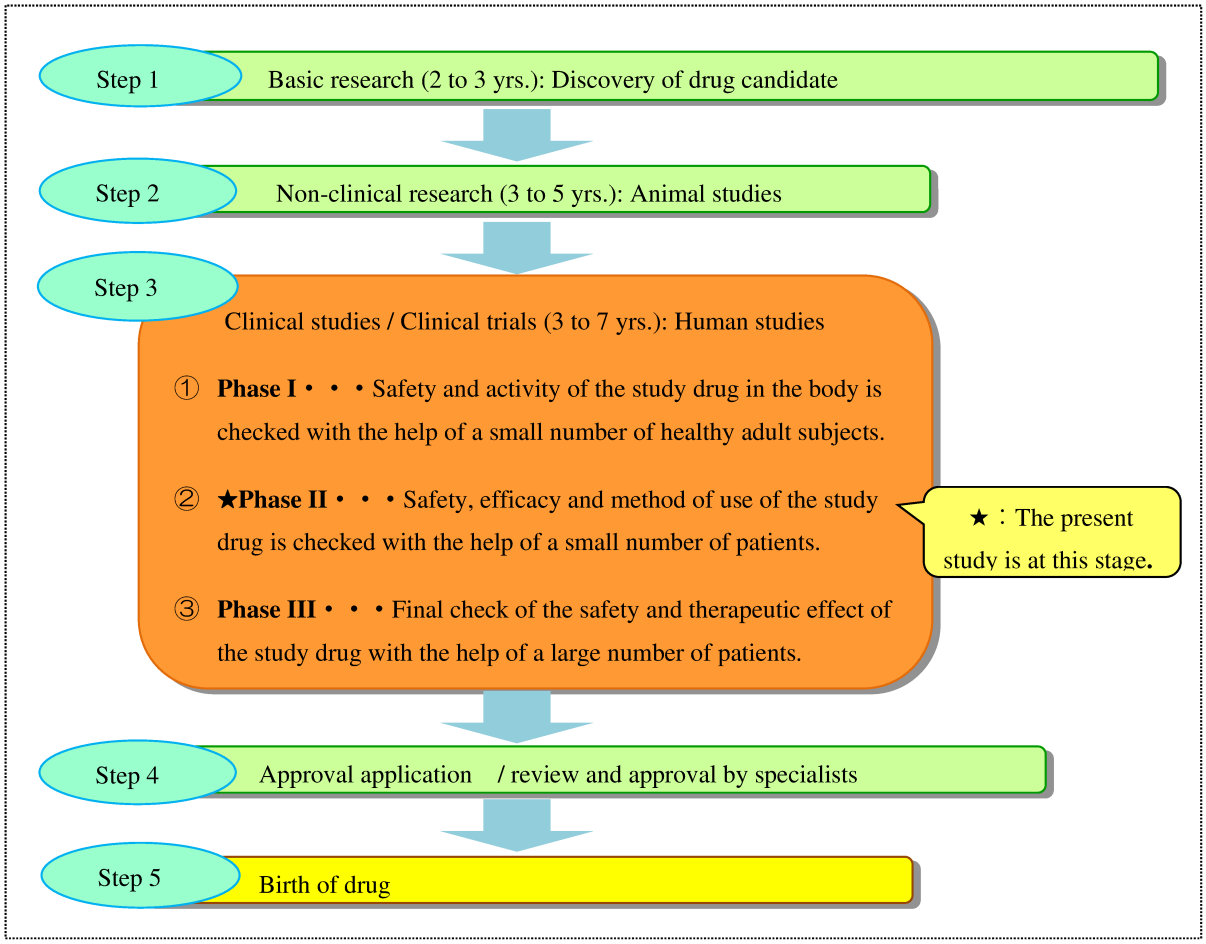

Figure 1-1 Flow of events leading to the birth of a new drug

In addition to the purpose of gaining necessary information for reviewing the drug, clinical trials also contain research aspects to it to gain new and unseen information. For this reason, clinical trials are conducted in accordance with the strict rules and standards stipulated by the government, and by thorough review and approval by an Institutional Review Board to ensure the scientific and ethical validity of the study plan, as well as its problem-free implementation. Please note that participation in a clinical trial will require you to make more hospital visits and undergo more tests than routine medical care.

Institutional Review Board (IRB)

This hospital has a clinical research review committee, or Institutional Review Board (IRB), which has been established by the director of the hospital and consist of physicians, other hospital staff and members of the general public that are outside of the hospital. This study has been reviewed and approved by this IRB to ensure that there are no scientific or ethical problems associated with it, and that the physician(s) involved with this study are eligible to do so. In addition, the IRB will examine the validity of continuing the study.

You can access the procedure manual and contents of review of the IRB on the website indicated below, and at the Office of Clinical Research Management. For details, please do not hesitate to contact the investigator or the Clinical Trial Help Desk.

＜Institutional Review Board of this hospital＞

Established by: Director of the Yokohama City University Hospital
Name: Yokohama City University Hospital IRB
Format: IRB established in the study site
Location: 3-9 Fukuura, Kanazawa-ku, Yokohama-shi, Kanagawa Prefecture
Website URL: http://www-user.yokohama-cu.ac.jp/~ynext/trial/irb/

3. About Your Disease (Symptoms)

The disease you have is called nonalcoholic fatty liver disease, where fat accumulates in the liver despite you not drinking much alcohol. It is thought to be caused by overeating, obesity and lack of exercise (a form of disease that is not caused by excessive consumption of alcohol). The disease can be classified into two types, the first being the “nonalcoholic fatty liver disease” that advances slowly, and the “nonalcoholic steatohepatitis” that advances rapidly and involves inflammation in addition to nonalcoholic fatty liver disease. In some cases, deterioration of the fatty liver disease can lead to liver cirrhosis and liver cancer.

4. About the Study Drugs “AJG533 (Elobixibat)” and “CTM27 (Cholestyramine)”

One of the study drugs that you will take upon agreeing to participate in this study, AJG533 (Elobixibat), has been approved in 2018 to be used to treat “Chronic constipation”. The other study drug, CTM27 (Cholestyramine), has been approved in 1984 to treat “Hypercholesterolemia”. These study drugs are expected to improve nonalcoholic fatty liver disease by preventing the absorption of bile acids by the body and quickening fat processing by the liver.

The present study will use drugs that contain the active ingredients of Elobixibat and Cholestyramine, as well as drugs that resemble but do not contain the active ingredients of Elobixibat and Cholestyramine (placebo drugs) as the study drugs.

5. Purpose of the Study

The purpose of this clinical trial is to investigate the efficacy and safety of the study

drugs by having patients of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis take the study drugs once a day. To be specific, we will make comparisons between patients that take either Elobixibat or Cholestyramine alone to patients that take placebo (drugs that resemble the actual drugs but contain no active ingredients), as well as comparisons between patients that take both Elobixibat and Cholestyramine to patients that take either Elobixibat or Cholestyramine alone. Please refer to "6. Study Methods (3) Method of use of study drugs" for details on how the drugs will be taken.

This hospital is the only site in which this clinical trial is being conducted, and we expect to recruit around 100 patients to participate in it.

The Elobixibat to be used in this study will be provided based on an appropriate agreement by EA Pharma Co., Ltd., who is selling a drug that has the same active ingredient. Furthermore, this clinical trial is being conducted with financial assistance from EA Pharma Co., Ltd. However, there will not be any changes made to your treatment or actions taken to compromise the impartiality of this study to favor the profits of EA Pharma Co., Ltd.

6. Study Methods

Criteria to participate in the clinical trial

(1) Clinical trial participation criteria

In order to carry out this study safely, those who participate must have fulfilled the conditions indicated below. Potential participants will be asked to undergo additional tests, and the investigator will ultimately decide if a patient can participate in the study. A patient may not be able to participate in the study depending on the outcome of these tests.

1) Individuals that can participate in the study

① A patient that is 20 to 75 years old at the time of consent

② A patient who can give his/her own written consent

③ A patient with definitive diagnosis of nonalcoholic steatohepatitis or suspected of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis based on a liver biopsy (a test takes a piece of liver tissue to diagnose the disease) within 8 months prior to the start of the screening period of this study

④ A patient whose liver fat mass as seen by MRI scans meets certain criteria

⑤ A patient whose fasting serum LDL cholesterol level meets certain criteria, or is receiving drug treatments for dyslipidemia

⑥ A patient capable of maintaining a stable diet and routine life during study participation

⑦ A patient deemed eligible by the investigator

2) Individuals that may be refused entry to study

① A patient that is pregnant, breastfeeding or may be pregnant at present time, or cannot agree to practice contraceptive methods during study participation

② A patient whose MR elastography results, BMI, hematological findings (liver function tests, platelets etc.) and urinalysis results fail to meet certain criteria

③ A patient with history of or complications with an acute or chronic liver disease that is not nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (active

viral hepatitis, cholangitis, bile duct obstruction, suspicion of hepatocellular carcinoma, Wilson disease, α1-antitrypsin deficiency, hemochromatosis or iron overload)

④ A patient with history of liver cirrhosis, HIV infection, type 1 diabetes, chronic pancreatitis, extensive colon/small intestinal surgery, Celiac disease

⑤ A patient with complications due to portal hypertension (ascites, hepatic encephalopathy, esophageal varices)

⑥ A patient that used drugs for treating nonalcoholic fatty liver disease for a period of 2 weeks or more during the one year leading up to the start of the study

⑦ A patient who has used ursodeoxycholic acid, thiazolidinedione, or any of the drugs known to have a significant effect on body weight before the start of the study

⑧ A patient that has used dyslipidemia medicines or oral diabetes medicines before the start of the study and has changed the doses used for them

⑨ A patient that fails to meet certain criteria regarding history of alcohol consumption

⑩ A patient who fails to meet certain criteria regarding the changes in body weight prior to the start of the study

⑪ A patient that has undergone surgery for obesity, or plans to do so during study participation

⑫ A patient with type 2 diabetes that his/her physician deems difficult to control

⑬ A patient with complications of hyperthyroidism or hypothyroidism, or thyroid

dysfunction, and fails to meet certain criteria

⑭ A patient with history of an illness associated with acute or chronic diarrhea

⑮ A patient whose blood pressure does not meet certain criteria

⑯ A patient who fails to meet certain criteria due to abnormalities of the heart or history of cerebral strokes

⑰ A patient with history of drug abuse during the one year leading up to the start of the study

⑱ A patient who has participated in another clinical trial during a certain period prior to the start of the study

⑲ A patient who has complications with malignant tumors

⑳ A patient who is unable to undergo MRI scans

㉑ A patient deemed ineligible by the investigator for other reasons

(2) Duration of study participation

Your participation in this study is scheduled to last a total of 26 weeks (up to around 6 months), which includes up to 8 weeks of Screening Period, 16 weeks of Study Drug Treatment Period and 2 weeks of Follow-up Period. Even if you discontinue your participation during the Study Drug Treatment Period, you will be asked to participate in the Follow-up Period (2 weeks after discontinuation).

(3) Method of use of study drugs

Once patients are confirmed to meet the "(1) Clinical trial participation criteria" prior to the start of the study, they are assigned to one of the following treatment groups and receive study drug treatments for 16 weeks. You will be randomly assigned to a group according to a predetermined selection method, and neither you nor the investigator will be able to choose the group to which you end up in. Furthermore, as study drugs are made to be indistinguishable from one another, you will know neither the identity of the drug nor the group to which you are assigned. This is to ensure the proper evaluation of the efficacy and safety of study drugs without the influence of preconception.

[Treatment Groups] There are 4 treatment groups.

Group 1	Elobixibat (Placebo) 2 tablets + Cholestyramine (Placebo) 2 sachets
Group 2	**Elobixibat 2 tablets** + Cholestyramine (Placebo) 2 sachets
Group 3	Elobixibat (Placebo) 2 tablets + **Cholestyramine 2 sachets**
Group 4	**Elobixibat 2 tablets + Cholestyramine 2 sachets**

[How to take the study drugs]

• You will be asked to come to the hospital 1 day before the start of treatments. You will start taking the study drugs from before breakfast on the following day, and continue to do so until before eating breakfast on the visit date 16 weeks later.

• You will be asked to take the study drug once a day, before breakfast. You will take 2 tablets of Elobixibat (including placebo) and 2 sachets of Cholestyramine (including placebo) each time.

• If you do not manage to take the study drugs at its intended timing, please take it within 12 hours or before 21:00, whichever is earlier.

• Please store the study drugs away from areas of high temperature and humidity.

(4) Schedule

After you agree to participate in this study, you will undergo tests and observations described in Table 6-1 according to schedule. In addition, you may be required to make additional visits, undergo additional tests and have additional blood samples taken aside from those which have been scheduled based on changes in your condition and by instruction of the investigator. The specific schedule is as outlined below.

1) Screening Period

If you provide your consent to participate in this study, you will be asked to undergo tests so that we may check that your present condition meets the criteria for you to participate in the study.

2) Treatment Period

Patients deemed eligible to participate in this study according to screening tests will be asked to take the study drugs. During the Study Drug Treatment Period, patients will undergo prescribed tests, and have their condition and clinical course of the disease checked to determine whether or not it is appropriate for them to continue in the study.

3) Follow-up Period

You will also be asked to undergo medical examinations and tests to check your condition 2 weeks after the end of study drug treatments.

4) Discontinuation

If you discontinue study drug treatments prematurely during the Study Drug Treatment Period, you will be asked to undergo medical examinations and tests when you stop taking the study drugs. In principle, you will also be asked to come to the hospital 2 weeks after discontinuation of treatment to undergo medical examinations and tests.

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Table 6-1. Study Schedule

Item	Before screening	Screening	Treatment					Follow-up
Weeks		-8 weeks to day before start of treatment	1 day before start of treatment	Week 4	Week 8	Week 12	Week 16/Discontinuation	End of treatment to 2 weeks
Tolerable range				±7 days	±7 days	±7 days	±7 days	±7 days
Consent	●							
Investigation of alcohol consumption history		●						
Chest X-ray		●						
ECG		●						
Height[1)]/Body weight/Waist/hip circumference/Waist/hip ratio		●	●				●	
Blood pressure/heart rate/respiratory rate/axillary body temp.		●	●	●	●	●	●	●
Pregnancy tests[2)]		●	●*				●	
MRI scans		●					●	
Liver biopsy[3)]		△						
Blood tests[4)]/Urinalysis		●	●*	●	●	●	●	●
Blood/fecal sampling for storage[5)]			○				○	
Questionnaire/Patient diary check			●	●	●	●	●	
Concomitant drugs		←						→
Adverse events		←						→

1) The height is only measured during screening.

2) Only the relevant female patients will undergo urinary pregnancy tests at screening, 1 day before start of treatment, and at Week 16 / Discontinuation.

3) Information will be collected for those who have results of a prior liver biopsy.

4) Blood sampling: Up to around 20 mL of blood will be taken each time, and up to around 100 mL of blood will be taken in total over the course of the study.

5) Blood and fecal samples for storage will be collected if you consent to providing them for exploratory research planned for the future. Up to around 20 mL of blood will

be collected. The blood and fecal samples collected will be used in exploratory research planned separately from this study, and approved by an ethics review committee that deliberates the implementation of said study from an independent and impartial standpoint. In this situation, your samples will be used to analyze inflammation after asking for your consent again. These samples will be stored for up to 5 years from the moment of their collection, and will be discarded according to appropriate methods thereafter.

*If there is data from less than one month ago, this will be used instead of conducting a new test.

7. Expected Benefits and Side Effects

＊Expected benefits

By using Elobixibat and Cholestyramine to suppress the absorption of bile acids by the body and quickening fat processing by the liver, we can expect to see improvements in nonalcoholic fatty liver disease.

＊Expected disadvantages

Although this study will assign each patient to a group to receive placebo, Elobixibat, Cholestyramine or combined Elobixibat + Cholestyramine, not all patients of all groups are guaranteed to see any therapeutic benefit. We do not expect patients that are assigned to the “Placebo group” to receive any therapeutic benefits of a drug.

In addition, clinical trials tend to involve more examinations and tests, and the examinations tend to take a lot of time. There are also drugs and treatments that you

cannot receive while you are participating in the study. Please notify the investigator in advance if you will receive any of the following drugs or treatments during your participation in this study.

[Drugs you cannot use during the study]

Drugs you cannot use during the study	Period
Bile acid preparations (ursodeoxycholic acid, chenodeoxycholic acid, dehydrocholic acid)	From screening to end of follow-up
Bile acid transporter inhibitors (Elobixibat) and anion exchange resin preparations (Cholestyramine, Colestimide) other than study drugs	
Thiazolidinedione	

[Treatments prohibited during the study]

Type of treatment	Period
Obesity surgery (sleeve gastrectomy, gastric bypass, sleeve bypass etc.)	From screening to end of follow-up

[Drugs that should be co-administered with great care during the study]

Type of drug	Period
Cardiotonic drugs (Digoxin, dabigatran etexilate methanesulfonate)	From the start to the end of study drug treatments
Aluminum-containing preparations	
Midazolam	
Anti-rheumatic drugs (methotrexate, salazosulfapyridine)	
Non-steroidal anti-inflammatory drugs	
Corticosteroids (hydrocortisone)	
Immunosuppressant drugs (Mycophenolate mofetil)	
Thiazide antihypertensive diuretic	
Chlorthalidone	

Type of drug	Period
Meticrane	
Mefruside	
Tetracycline	
Phenobarbital	
Vancomycin hydrochloride	
Thyroid hormone preparations	
Raloxifene hydrochloride	
Fibrate drugs	
Warfarin	
Fluvastatin sodium etc.	
Ezetimibe	
Acarbose	
Spironolactone	

[Drugs whose method of use cannot be changed or whose use cannot be newly started during the study]

Type of drug	Period
Antihypertensive drugs (angiotensin II receptor antagonist only)	From 4 weeks before enrollment to the end of study drug treatments
Vitamin E	
Dyslipidemia medication	
Diabetes medication (DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, insulin injections)	

＊Side effects

Various studies have been conducted in Japan and abroad using Elobixibat and Cholestyramine, and the following side effects have been observed in these studies. It does not mean that all side effects would manifest in all patients. On the other hand, it

is possible that side effects other than those listed here would appear, and the possibility cannot be ruled out that some side effects can be life-threatening.

○Safety information about Elobixibat being marketed in Japan (product name: Goofice tablet 5 mg)

Elobixibat is a drug that is already being sold in Japan for the purposes of improving the symptoms of chronic constipation, and its use is associated with side effects described below. As such, similar side effects may appear.

In Japanese clinical studies conducted until drug approval, 292 out of 631 subjects (46.3%) experienced side effects of the drug. The main side effects that appeared were abdominal pain in 120 subjects (19.0%), and diarrhea in 99 subjects (15.7%).

Although there were no serious side effects, the other side effects observed were as shown below, according to their frequencies.

	5% or more	1 to 5%	Less than 1%
Liver		Liver function test abnormalities (increased ALT and AST)	
Psychological / Neurological			Headaches, dizziness
Circulatory			Hot flashes
Gastrointestinal	Abdominal pain (19.0%), diarrhea (15.7%), lower abdominal pain, abdominal distension	Nausea, upper abdominal pain, abdominal discomfort, soft stool	Bloating, dry mouth, defecation urgency, vomiting, abnormal intestinal sounds, constipation, stomatitis
Hypersensitivity			Hives, rash
Blood			Increased eosinophils, anemia, increased Vitamin E
Other		Increased CK	Dysmenorrhea

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○Safety information about Cholestyramine being marketed in Japan (product name: Questran powder 44.4%)

Cholestyramine is a drug that is already being marketed in Japan for improving the symptoms of hypercholesterolemia in adults, and its use is associated with side effects described below. As such, similar side effects may appear.

In Japanese clinical studies and drug use surveys conducted until drug approval, 272 out of 1,594 subjects (17.1%) experienced side effects of the drug. The main side effects that appeared were constipation in 174 subjects (10.9%) and increased ALT in 85 out of 1,369 subjects (6.2%).

Intestinal obstruction (frequency unknown) was observed as a serious side effect, and the other side effects observed were as shown below, according to their frequencies.

	5% or more	0.1 to 5%	Less than 0.1%
Gastrointestinal	Constipation	Hard stool, gastric/abdominal distension, abdominal murmurs, loss of appetite, nausea and vomiting, diarrhea, soft stool, abdominal pain, epigastric pain, gastric/abdominal discomfort, heartburn	Gastric ulcers, gingival swelling
Liver	Increased ALT	Increased AST, increased Al-P, increased LDH, increased total bilirubin, abnormal liver function	
Kidneys		Increased BUN, increased creatinine	
Blood		Increased white blood cells, decreased hemoglobin, decreased hematocrit	
Skin		Rash, pruritus	Facial flush, heat sensation, erythema
Muscles		Increased CK	
Other		Oral aphtha, increased serum potassium/phosphorus/uric acid, decreased serum potassium/calcium/Vitamin D	Lightheadedness, headaches, vitreous hemorrhage, tinnitus, capillary expansion, urinary disorder, fatigue

Not all patients necessarily experience these side effects. Please notify the investigator immediately if you notice any changes to your condition or symptoms that bother you. You will receive appropriate treatments for it. Regular tests and examinations will be carried out during the study to check for the appearance of such undesirable symptoms. Unforeseeable side effects other than those listed here may appear. Please speak to the investigator at any time to find out about the latest information related to side effects.

8. When New Information about the Study Becomes Available

If any changes will be made to the plan of this study, you will receive explanations about what is being changed.

In addition, should we obtain new information that can affect your wish to participate in this study during the study, such as information about new side effects, we will notify you about it immediately. In these situations, we will ask you again if you wish to continue participating in the study.

However, as described in "9. Discontinuation of the Study", the decision to participate in this study is entirely yours. As such, you may withdraw yourself from the study at any time.

9. Discontinuation of the Study

Even if you start participating in this study, the study may be discontinued in the following situations:

(1) Discontinuation of the clinical trial itself

1) Due to unavoidable circumstances that affect the safety of patients, or the ethical or medical aspects of the study
2) Due to loss of scientific validity for developing this drug
3) Due to hindrance of proper conduct of the clinical trial resulting from violation of ministerial ordinances, study plans and various procedures that the Principal Investigator or study site should abide by
4) Due to decision by the Principal Investigator to terminate or suspend this study
5) Due to an instruction by the IRB to terminate the study

(2) Discontinuation of your participation in the study

1) Due to your request to withdraw from the study
2) Due to test results and your symptoms not conforming with the conditions for you to participate in the study
3) Due to your poor physical condition that makes it difficult for you to continue the study
4) Due to other reasons for which the investigator recommends the discontinuation of your participation

If your participation in the study will be discontinued after you start the use of study drugs, please cooperate with the tests indicated by ● in the "Week 16/Discontinuation" column on "Table 6-1. Study Schedule".

Furthermore, you will not be disadvantaged or mistreated in any way in receiving your subsequent treatments, even if you discontinue your participation in the study. The best available treatment will be chosen to treat your disease. Please note that results of the study associated with you may continue to be used even after your withdrawal from the study.

10. Alternative Treatments

At present time, there is no insurance coverage in Japan for drugs that treat nonalcoholic fatty liver disease, and common approach to treat the disease is by improvement of lifestyle habits through diet and exercise therapy. This may improve background conditions such as obesity, diabetes, dyslipidemia and hypertension etc., and lead to improvements in nonalcoholic fatty liver disease as well. Although drugs for hypertension, dyslipidemia or diabetes are used indirectly to treat this condition if improvements in lifestyle habits do not lead to sufficient improvements in the condition, it is not clear whether these drugs can be effective in the long run. You will be able to

discuss with your doctor to choose a treatment that suits you best, regardless of whether you decide not to participate in this study or discontinue your participation in the study prematurely.

11. Health Injuries

If you notice any unusual symptoms during your participation in the study, please contact the investigator right away. Appropriate intervention and treatments will be given to you.

If you experience any health injuries such as side effects etc. during the study or after the end of the study as a result of your participation in the study, the investigator will make arrangements for you to receive the best available treatment for it. You may also be able to receive compensation for the health injuries. However, if the health injury resulted from you ignoring the investigator's instructions, or due to your negligence or intentional doing, as well as if it is learned that the health injury is unrelated to the study, your compensation may be void or restricted.

Please also remember to store the medical bills issued by the medical institution safe to receive compensation.

Please see the attachment ("Compensation for Health Injuries") for details about compensation.

12. Reducing Financial Burden associated with Study Participation

You will not be charged anything for the study drugs that you will take during the

study. They will be provided to you free of charge. However, you will have to pay for the insured medical treatment costs related to the medical examinations (blood tests, MRI scans, etc.) performed at this hospital as well as drug charges other than the study drugs.

This hospital will pay you 10,000 JPY per visit as burden-relieving payments to reduce your financial burden, such as transportation costs. You may be paid up to 70,000 JPY in total, according to the number of study visits you complete. These payments will be paid altogether to an account designated by you, from “Yokohama City University”. Please read the separate written information document related to the receipt of Clinical Trial Collaboration Fees.

You may opt out of receiving these payments for whatever reason.

13. Personal Information

In order to check that this study has been conducted properly, study-related personnel may access your medical records that are related to the study (medical charts etc.), even in situations where you prematurely withdraw from this study. Study-related personnel include employees of companies contracted by the Principal Investigator, members of the IRB, officers/employees of the Ministry of Health, Labour and Welfare, as well as individuals contracted by the government to carry out investigations. These individuals are mandated by law to maintain the confidentiality of the contents of records such as medical records that they access, which means that information related to your privacy will not be leaked outside the hospital.

The results of this study may be reported to the company selling the drug that has the

same ingredient as AJG533 (Elobixibat), and may be used as part of the data to be submitted to the government (MHLW). Furthermore, data obtained from this study may be presented in medical journals and conferences. Furthermore, information specific to you in the clinical trial report will use an identifier code that is a combination of numbers and letters, rather than personal information about you such as names and address etc. The list that links your identifier code to your name etc. will be kept and managed in the hospital, in accordance with rules related to the hospital's personal information management. However, information such as the date of birth that is part of the personal information, although mentioned in clinical trial reports for the purposes of checking the clinical trial participation criteria etc., will not be leaked to the outside or be used for purposes other than the study. Sufficient care will be taken to protect your privacy when handling your personal information.

Please understand that, by listening to this explanation and signing this consent form, you will be agreeing to such access to medical records and use of personal information (date of birth, etc.).

14. Your Responsibilities

Please follow the instructions below to ensure your safety, and for us to collect reliable data.

(1) You will be required to fast for 8 hours prior to the blood tests that will be conducted during Week 4, 8, 12, and 16 Visits, as well as at the time of Discontinuation. For this reason, please take the study drugs at the following timing:

• If you will be examined during the morning, please come to the hospital after having taken the study drugs and without eating breakfast.

• If you will be examined during the afternoon, please take the study drugs at the

same timing before breakfast, and come to the hospital without eating lunch. Furthermore, as it is necessary that you fast from 8 hours prior to the blood tests, you may need to come to the hospital without eating breakfast, depending on the timing of your meals.

(2) Please maintain stable diet and normal life (exercise level) during your participation in the study.

(3) If you will seek medical attention at another hospital, please notify the attending doctor that you are participating in a clinical trial. Please also notify the investigator or the Clinical Research Coordinator that you were examined by another doctor. With your permission, we may contact the doctor at the other hospital about your symptoms and medicines taken.

(4) Please comply with all scheduled study visits. (Please notify us in advance if there is a scheduling clash.)

(5) Please discuss with the investigator in advance if you are currently using other medicines (including over-the-counter drugs and health foods), will start using new medicines after beginning study participation, or receive new treatments other than drugs. (Depending on the drug, they may interact with the study drugs and reduce or intensify the effect of the study drugs.)

(6) Please contact the investigator at any time if you notice that your condition is unusual (including bone fractures and accidents).

(7) On study visit dates, please bring your patient diary, remaining study drugs, packets of study drugs and empty study drug sheets with you.

(8) If you are a woman of childbearing potential, please practice contraceptive methods during your participation in the study. Please discuss with your investigator to select a contraceptive method that suits you best. Please notify us immediately if you think that the contraceptive method did not work well, or you think you may have become

pregnant.

(9) Please be sure to notify the investigator if there are any changes to your contact information such as address and telephone number.

15. Disaster Emergency Message Dial during Large-Scale Disasters

We may contact the telephone number that you provide us in advance to check your safety (including family members) in the event of a large-scale disaster. If the communication line stagnates, please cooperate by using the Disaster Emergency Message Dial number “171”.

The Disaster Emergency Message Dial has been established with the intent to be used 30 minutes after the incidence of an earthquake that has a seismic coefficient of 6 or higher, and it is a service that allows you to convey safety from disaster-affected sites using telephones and the Internet.

[How to record on the Disaster Emergency Message Dial “171”]

① Dial “171”, and listen to the guidance

② Dial (1) (Record)

③ Dial your home telephone number (City Code • ○○○○-○○○○).

④ You will be asked to indicate the type of your telephone device (push-button or dial phone).

⑤ Please record your name and contact information according to the guidance provided.

[How to replay a message on Disaster Emergency Message Dial "171"]

① Dial "171", and listen to the guidance

② Dial (2) (Replay)

③ Dial the telephone number of the person you wish to contact (City Code • ○○○○-○○○○).

④ You will be asked to indicate the type of your telephone device (push-button or dial phone).

⑤ The latest message will be played first.

[Broadband message board "web171" for disasters]

① Search Web171 and access the website https://www.web171.jp/

16. Clinical Trial Help Desk

Yokohama City University Hospital

(1) Name of Principal Investigator: Takaomi Kessoku, Assistant Professor

Name of Your Investigator:

Tel.: 045-787-2800

(2) Help Desk: Yokohama City University Hospital

Office of Clinical Trial Management

Tel.: 045-352-7510 (Weekdays from 9:00 to 17:00)

(3) Contact Information at Night-times / Holidays

Tel.: 045-787-2800 (Main Number)

*Please contact the above number at night-times, holidays and at times of emergency, and speak to the on-call doctor of the Department of Gastroenterology.

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Date prepared: February 20, 2020

Attachment 1 **Explanation of Terminology**

No.	Term	Explanation
1)	Liver cirrhosis	A disease in which inflammation occurs in cells of the liver, and repeated repairing of inflammation leads to the liver hardening and losing its function.
2)	Liver cancer	A disease in which liver cells become cancerous.
3)	Chronic constipation	A condition where constipation symptoms such as the reduced frequency of bowel movements and fecal quantity persist for a long period of time.
4)	Hypercholesterolemia	A condition where cholesterol concentration in the blood is high.
5)	Leflunomide	A drug used to treat rheumatoid arthritis.
6)	Active metabolites	New substance(s) generated from the metabolism of another.
7)	Placebo	A mimetic drug that does not contain the active ingredient of the drug, and its appearance is indistinguishable from the active study drug. It is believed that by giving some study participants a placebo, it is possible to more accurately determine how “real” the efficacy and safety of the study drug is.
8)	Liver biopsy	A test that diagnoses a disease by cutting a piece of the liver and examining it.

No.	Term	Explanation
9)	MRI scans	A test that has the patient enter a tube made of a powerful magnet in order to take images of the organs and blood vessels in the body using magnetism.
10)	Liver fat mass	A number that indicates how much fat is on the liver.
11)	Fasting serum LDL-cholesterol	A type of fat found in the blood while fasting.
12)	Dyslipidemia	A condition where levels of lipids such as cholesterol and neutral fats contained in the blood are above certain criteria.
13)	MR elastography	A test where vibration is applied to the liver, and the vibrating liver is pictured by MRI to measure the hardness of the liver.
14)	BMI	This is short for Body Mass Index, which is calculated based on the relationship between body weight and height, and indicates the degree of obesity.
15)	Wilson disease	A disease that is caused by a genetic abnormality, which results in improper excretion of copper, and subsequently its accumulation in the body.
16)	α1-antitrypsin deficiency	A disease where lack of α1-antitrypsin in the body results in various abnormalities in the lungs such as dyspnea and cough.

No.	Term	Explanation
17)	Hemochromatosis	A disease where something causes abnormal increase in iron levels in the body that results in adverse effects on various organs, and destroys cells and tissues to disrupt organ function.
18)	HIV	A virus that infects human immune cells and causes acquired immunodeficiency syndrome (AIDS).
19)	Celiac disease	A disease where an erroneous immune reaction to “Gluten” contained in wheat results in various adverse effects to the small intestines.
20)	Ascites	A disease where more water than usual is retained in the peritoneum that wraps the abdominal organs. Although there are various causes to this, liver cirrhosis and inflammatory diseases make this easier to happen.
21)	Hepatic encephalopathy	Reduced liver function leads to accumulation of unnecessary substances in the blood, and these substances adversely affect the brain to produce symptoms like consciousness disorders.
22)	Esophageal varices	A condition in which the veins on the mucous membrane of the esophagus thickens and appears like a lump. This tends to occur in patients with increased pressure on the “Portal vein” that carries nutrients to the liver, and patients with liver cirrhosis.

No.	Term	Explanation
23)	ALT	An enzyme that is normally present inside the cells. Its level in the blood increases when there is something wrong with the liver.
24)	AST	An enzyme that is normally present inside the cells. Its level in the blood increases when there is something wrong with the liver, heart and muscles.
25)	Abdominal distension	When the stomach feels expanded.
26)	Nausea	A bad feeling that makes you want to vomit.
27)	Bloating	When the stomach swells up due to gas accumulation in the gut.
28)	Dry mouth	Feeling of thirst.
29)	CK	This is short for creatine kinase, which is an enzyme that is found in abundance in the muscles and brain. The level of CK in blood rises when there is inflammation in these tissues.
30)	Epigastric pain	Pain in the pit of the stomach.
31)	Al-P	An enzyme that is normally present inside the cells. Its level in the blood increases when there is something wrong with the liver or bones.

No.	Term	Explanation
32)	LDH	An enzyme that is normally present inside the cells. Its level in the blood increases when there is something wrong with the liver or muscles.
33)	Bilirubin	A pigment released when red blood cells are destroyed. Its level rises in liver diseases.
34)	BUN	A type of waste product of substances used in the body. Its level in the blood and urine rises when there is inflammation in the kidneys, or the kidney functions deteriorate.
35)	Creatinine	A type of waste product of substance used in the body. Its level in the urine rises when kidney functions deteriorate.
36)	Hemoglobin	A protein contained in blood. It has the role of carrying oxygen from the lungs to all over the body.
37)	Hematocrit	This indicates the ratio of volume of red blood cells in the blood. Its level decreases when the patient has anemia.
38)	Rash	When red bumps appear on the skin.
39)	Pruritus	When the skin feels itchy.

No.	Term	Explanation
40)	Gastric ulcer	A condition in which the wall of the stomach is injured. It can cause symptoms like abdominal pain and anemia due to bleeding.
41)	Gingival swelling	The swelling of gums caused by bacterial infection or malnutrition.
42)	Erythema	Red spots forming on the skin.
43)	Oral aphtha	These are generally called stomatitis, and refer to blotches that develop in the mouth.
44)	Serum potassium	A substance called potassium in the blood.
45)	Serum phosphorus	A substance called phosphorus in the blood.
46)	Serum uric acid	A substance called uric acid in the blood.
47)	Vitreous hemorrhage	Bleeding on the inner side of the eye. This may deteriorate the vision.

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Attachment 2 **Compensation for Health Injuries**

A Phase II Investigator-led Study to Compare the Efficacy and Safety of Combined Elobixibat and Cholestyramine to that of Placebo, Cholestyramine Monotherapy or Elobixibat Monotherapy for Nonalcoholic Fatty Liver Disease

(Investigator-led Clinical Trial)

Although this clinical trial will be carried out with the utmost care, we have established guidelines and procedures in the event that you suffer health injuries as a result of taking the study drugs or participating in the study.
The purpose of this document is to provide detailed explanations for the contents related to compensation mentioned in the Informed Consent Form. Please keep this document safe along with your copy of the ICF.

If you notice any health injuries such as side effects, please do not hesitate to notify the investigator or a clinical trial collaborator. Treatments and other appropriate measures thought to suit you best will be taken.

1. Compensation for health injuries that occur in this study

(1) Principle of compensation

1) Compensation is to appropriately cover for damages in the event you suffer a health injury, in accordance with the GCP Ordinance (rules stipulated by the government for when clinical trials are conducted), even if the medical institution has no legal liability (when there is no negligence) for the health injury.

2) If you experience a health injury as a result of your participation in this study, you will be compensated based on the guidelines and procedures for compensation.

3) If liability is discovered, you may file a claim for damages. This compensation system does not prevent you from exercising your right to claim damages.

(2) Criteria for compensation

The compensation provided in this study include disability compensation and bereaved family compensation in the event of residual sequelae (Grade 1 to 3) and death, respectively. There will be no payments towards medical expenses and medical allowances in this study.

Health injuries other than sequelae (Grade 1 to 3) and death will be compensated in the form of provision of medical care. As medical expenses incurred at that time will be paid by your health insurance program, you will be asked to pay part of the costs.

(3) Situations that are not compensated for

1) You cannot receive compensation if there is no causal relationship between your health injury and this study.

2) You cannot receive compensation if the hospital, the investigator at this hospital and another third party has legal liability for your health injury, and the responsible party should pay for the damages caused.

3) You cannot receive compensation for health injuries that occurred because of your intentional doing.

(4) Situations when compensation is limited

The compensation payment may be reduced in amount or void altogether if the health injury occurs as a result of your gross negligence (lying or making false reports, failure to follow the instructed dosage and administration, failure to listen to the instructions of the investigator etc.).

2. Compensation procedures

(1) What to do if you experience a health injury

If you experience some form of a health injury as a result of this study, this hospital will provide treatments and take other measures considered most suitable for you.

(2) Request for compensation

Please notify the investigator or the clinical trial collaborator, if you feel you have suffered a health injury, such as side effects etc. The Principal Investigator will determine the causal relationship between the health injury and the study, before explaining to you whether or not you can receive compensation for your health injury.

Please do not hesitate to ask the investigator about any other questions you may have about compensation.

3. Treatment of personal information

Personal information about you collected in the process of providing compensation will be managed and treated appropriately according to the “Personal Information Protection Law”, and will not be used for any purposes other than compensation.

4. Other

Please do not hesitate to contact the investigator, clinical trial collaborator or the Clinical Trial Help Desk listed in the written information document, if you have any questions regarding compensation.

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Consent Form

Reference No.:（19-466） [Copy for Medical Chart (Physician)]

Herewith I provide my voluntary consent to participate in the clinical trial titled [A Phase II Investigator-led Study to Compare the Efficacy and Safety of Combined Elobixibat and Cholestyramine to that of Placebo, Cholestyramine Monotherapy or Elobixibat Monotherapy for Nonalcoholic Fatty Liver Disease], after being given explanations about this study and having thoroughly understood what was explained to me. I will also receive and store a copy of the written information document and this consent form.

Signature of the Clinical Trial Participant

Date of Consent: __/__/____ Patient Signature：_____

Do you wish to receive burden-relieving payments for study participation? (Yes / No)

Do you consent to providing blood samples for exploratory research? (Yes / No)

Do you consent to providing fecal samples for exploratory research? (Yes / No)

Signature of Physician Handling Informed Consent Process

Date of Explanation: __/__/____ Physician Signature：_____

Signature of Collaborator Providing Supplementary Explanations

Date of Explanation: __/__/____ Collaborator Signature：_____

Date of Issue of Consent Form: __/__/____

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Consent Form

Reference No.: (19-466) [Copy for Office of Clinical Trial Management]

Herewith I provide my voluntary consent to participate in the clinical trial titled [A Phase II Investigator-led Study to Compare the Efficacy and Safety of Combined Elobixibat and Cholestyramine to that of Placebo, Cholestyramine Monotherapy or Elobixibat Monotherapy for Nonalcoholic Fatty Liver Disease], after being given explanations about this study and having thoroughly understood what was explained to me. I will also receive and store a copy of the written information document and this consent form.

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Do you consent to providing blood samples for exploratory research? (Yes / No)

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Signature of Physician Handling Informed Consent Process

Date of Explanation: __/__/____ Physician Signature：_____

Signature of Collaborator Providing Supplementary Explanations

Date of Explanation: __/__/____ Collaborator Signature：_____

Date of Issue of Consent Form: __/__/____

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Consent Form

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Signature of Collaborator Providing Supplementary Explanations

Date of Explanation: __/__/____ Collaborator Signature：_____

Date of Issue of Consent Form: __/__/____