Informed consent form To Patients

—A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Comparative Study to Evaluate the Efficacy and Safety of AJG533 (Elobixibat) in the 12-week Treatment of Patients with Chronic Constipation—

1 Introduction

Research conducted on human subjects to elucidate the causes of diseases and to improve prevention, diagnosis, and treatment methods is called “clinical research. In modern medicine, the causes of diseases and treatment methods have been elucidated through the accumulated results of clinical research to date. Clinical research is indispensable for the further advancement and development of medical care and for more effective and safer medical treatment. To conduct clinical research, we need the understanding and cooperation of many patients.

I will explain the contents of the research, your interests and rights, and other necessary matters based on this explanation document. Please read this document carefully and make sure you fully understand the contents.

Please read the contents carefully, understand them fully, and decide of your own free will whether or not to participate in this research. Please consult with your family and

You may consult with a family member or friend and respond at a later date. If you have any questions, please do not hesitate to ask.

If you have any questions, please do not hesitate to ask.

2 The name of the specific clinical research to be conducted, the fact that permission to conduct the specific clinical research has been obtained from the administrator of the implementing medical institution, and that the implementation plan has been submitted to the Minister of Health, Labour and Welfare.

2.1 Name of the specific clinical research to be conducted

A multicenter, randomized, placebo-controlled, double-blind, comparative study to evaluate the efficacy and safety of 12-week treatment with AJG533 (elobixibat) in patients with chronic constipation
2.2 Approval of the administrator of the performing institution
Since clinical research is conducted on patients, it is important to ensure that the human rights of patients are protected, that the safety of patients is ensured, and that there are no problems in conducting the research. Therefore, the implementation of the research must be reviewed from ethical and scientific perspectives to ensure that the human rights of patients are protected, that the safety of patients is ensured, and that there are no problems with the research. The research will be conducted in accordance with the law (Clinical Research Law) established by the Japanese government, and will be reviewed from ethical and scientific perspectives. The research will be conducted in accordance with the law (Clinical Research Act) established by the Japanese government. The research will be conducted in accordance with the law (Clinical Research Act) established by the Japanese government. The research has been rigorously reviewed and approved by the Clinical Research Review Committee accredited by the Minister of Health, Labour and Welfare, and has been approved by the hospital director of this hospital.

2.3 That the implementation plan has been submitted to the Minister of Health, Labor and Welfare
The clinical research described hereafter is subject to approval by the hospital director and submission of a plan (implementation plan) to the Minister of Health, Labour and Welfare for the implementation of the clinical research. The clinical research plan (implementation plan) is submitted to the Minister of Health, Labour and Welfare after obtaining the approval of the hospital director.

2.4 Agreements
You must fully understand the explanations in this document and give your consent to participate in this study in writing. You are asked to freely and voluntarily give your consent to participate in this research in writing after fully understanding the explanations provided in this document.

2.5 Purpose and Significance of Clinical Research
2.5.1 Purpose
Constipation is more common in women than in men and increases with age. Symptoms include abdominal discomfort, difficulty in defecation. Symptoms include abdominal discomfort, difficulty in defecation, and a feeling of residual stools. However, if left untreated, the disease can become a serious problem in daily life. However, if left untreated, it can interfere with daily life and cause other diseases. It is important to correct the symptoms. Treatment consists of dietary and lifestyle modifications and, if not sufficiently
effective, drug therapy. There are various types of medications available, but each has its own side effects. They also have problems such as dependence and diminishing effects when taken over a long period of time.

In this study, we used Elobixibat (product name: Gufis Tablets 5 mg), which is already approved as a medication for constipation. (product name: Gufis Tablets 5 mg), which is already approved as a medication for constipation, will be used as the study drug. The study will use Elobixibat (product name: Gufis Tablets 5 mg) as the study drug. The patients will take either a placebo or the research drug for 12 weeks to investigate the efficacy and safety of the drug over a long period of time. The safety and efficacy of the drug will be investigated.

### 2.5.2 Significance

The research drug Elobixibat is approved for the treatment of chronic constipation and is marketed under the brand name Gufis. It is marketed under the brand name Goofy’s Tablets 5 mg. This elobixibat promotes the effect of defecation through two actions: the secretion of water and the promotion of colonic motility by bile acids that flow into the colon.

To date, the effects of short-term administration have been tested in clinical trials, but 12-week administration has not been tested. 12-week dosing can lead to problems such as dependence and reduced efficacy, which can lead to changes in the therapeutic agent and affect daily life due to inadequate satisfaction. This study will compare and evaluate the efficacy, safety, etc. of the medication when taken over a long period of time, compared to placebo, leading to a satisfactory treatment effect for patients.

### 3 Methods and Duration of Clinical Research

If you agree to participate in this study, we will conduct an examination and medical examination to determine if you meet the criteria for participation in this study. If you agree to participate in this study, you will undergo an examination and a medical examination to determine whether you meet the criteria for participation in this study. Only those who are deemed fit to participate in the study will be asked to participate in the study.

Details of the research methodology (research schedule, investigations and tests to be conducted during the study) and time frame will be explained in more detail later in this document, will be explained in detail later.
3.1 Reasons for selection as a subject for specific clinical research
This study is for people with chronic constipation and there are criteria for participation in the study.
Your physician will make the final determination as to whether you meet the criteria for participation in the study.

■ Eligibility Criteria
① Those diagnosed with chronic constipation
② 20 years of age or older and 85 years of age or younger at the time of obtaining consent.
③ Able to keep a patient diary record during participation in the study.
④ Those who have received written consent from the person in question
⑤ Those who are deemed eligible by the physician in charge

■ Criteria for those who may be excluded from participation
① Those who are constipated or suspected to be constipated due to a disease of the intestines themselves.
② Those who have, or are suspected to have, difficulty in passing through the intestines due to poor bowel movement.
③ Those with or suspected of having prolapse
④ Patients who have undergone laparotomy within 12 weeks prior to obtaining consent (excluding appendicitis surgery)
⑤ Patients who have had a gall bladder resection or a procedure using an endoscope, etc.
⑥ Patients with complications of malignant tumors. However, this excludes those who have undergone surgery and treatment has been completed, and those who have undergone chemotherapy and radiotherapy treatment.
⑦ Pregnant, lactating, possibly currently pregnant, or unable to agree to use contraception while participating in the study.
⑧ Patients with serious diseases of kidney, liver, or heart
⑨ Patients with drug allergies to this research drug
⑩ Those who meet the contraindications for the remedy (bisacodyl suppositories and prussenide tablets).
However, if any of the relief medications are not contraindicated, participation is permitted.
⑪ Those who are participating in clinical research other than this study or who have participated in other research within 4 weeks prior to obtaining consent.
⑫ Other patients deemed ineligible by the physician in charge
3.2 Duration of participation in the study

The duration of participation in this study will be 2–4 weeks of observation and 12 weeks (maximum 13 weeks) of taking the study medication, for a total of approximately 14 weeks (maximum 17 weeks).

3.3 From the observation period to the end of the treatment period

If you are determined to be eligible to participate in this study, you will be asked to stop taking the laxatives you have been taking before the start of the observation period. You will be asked to stop taking the laxatives you have been taking prior to the start of the observation period. Instead, you will be required to use a remedy (bisacodyl suppository 10 mg or prussenide tablets 12 mg) from the beginning of the observation period until the end of the treatment period, according to the following conditions. A daily patient diary will be kept during this period.

 Dosage per dose: Bisacodyl suppository 10mg 1 unit
Pulsenide tablet 12 mg 2 tablets

• Only if there is no defecation for more than 2 consecutive days, a single dose of relief medication (bisacodyl suppositories or prussenide tablet) can be used for one dose.
• If you have no bowel movements after using bisacodyl suppositories or prussenide tablets, tell your doctor. If you do not have a bowel movement after using bisacodyl suppositories or prussenide tablets, tell your doctor.
• If you have a bowel movement after using a remedy and then do not have a bowel movement for more than 2 consecutive days, you can use one additional dose of the remedy again. If the patient has a bowel movement after using the remedy and does not have a bowel movement for at least two consecutive days, the remedy can be used again for one additional dose.
3.4 Allocations and their proportions, etc.

After the observation period, patients who meet the criteria for participation in the treatment period (dosing initiation criteria) will be assigned to one of the following groups at a ratio of 1:1. After the observation period, those who meet the eligibility criteria to participate in the treatment period (starting criteria) will be assigned to one of the following groups at a ratio of 1:1.

1. Group taking placebo
2. Groups taking research drugs

Grouping is done by a method called “randomized (randomization) assignment”. This is a method in which the grouping is done randomly, using a computer or other means, in a way that does not involve human intention. Neither you nor your doctor can choose which group you will be placed in. Therefore, there is a possibility that you may not be assigned to the group of your choice.

Also, if you know which group you are assigned to, your assumptions may change the way the medication works. For example, because you are taking a research drug, side effects may change because you are taking a research drug, or that it may not work because you are taking a placebo. For example, if you are taking a research drug, you may experience more side effects. To remove the influence of these assumptions, we will ask you which group you have been assigned to. To eliminate the influence of these assumptions, we will conduct the study without informing you or your doctor which group you have been assigned to. However, in the case of an emergency, we will reveal your group assignment to you.

In case of emergency, however, we can reveal your group assignment to you so that you can receive treatment or treatment or procedure.

3.5 Placebos (medications that do not contain any medicinal ingredients)

A placebo is a fake drug that looks (looks) the same as the research drug. Elobixibat, but does not contain the active ingredient of the drug, making it indistinguishable from the research drug in appearance. Therefore, your doctor, research staff, or anyone else will not know which research drug you are taking.

3.6 Schedule of the study

The schedule for this study is shown in the table. After obtaining your consent, you will be asked to visit the clinic a total of five times before the end of the treatment period. However, several more visits may be necessary depending on the results of tests and other tests.

During the study, you will start taking either placebo or research medication from...
V2 (allocation) and take it once a day before meals for 12 weeks. During this time, you will undergo examinations, medical examinations, etc. according to the following schedule.

**Schedule**

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Informed consent</th>
<th>Observational period</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Window</td>
<td>Registration</td>
<td>V2: Randomisation</td>
<td>V3</td>
</tr>
<tr>
<td>-</td>
<td>2–4 weeks after registration</td>
<td>± 7 days</td>
<td>± 7 days</td>
</tr>
<tr>
<td>Informed consent</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs, height and weight</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Blood test</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registration</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmation of administration start criteria allocation</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and stool collection for exploratory research</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Providing drugs</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Checking the medication status</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review concomitant medications</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Review rescue drugs</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Review adverse events</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaire/Review patient diary</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>Patient diary confirmation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Height and weight will be conducted only at the time of registration.

** A patient diary is to be kept daily from the beginning of the observation period to the end of the treatment period and is to be brought to the next visit.

● A stool collection kit will be given to you in advance (at the previous visit). You will be asked to bring the collected stools to the next visit. The next time you come to the clinic, you will be asked to bring the stool samples with you.

### 3.7 Survey Contents

Subject Background :
We will ask about any previous illnesses or surgeries you have had, complications, and allergies. Vital signs/height Weight: blood pressure, pulse Height and weight are measured only at registration.

subjective symptoms and other findings:
We will ask you about your physical condition during the consultation.

blood test:
White blood cell count, hemoglobin, platelet count, total protein, albumin, liver function, renal function. 
Lipids, Electrolytes 
The volume of blood drawn is 10 mL at a time, for a total of 20 mL (10 mL x 2 times total) during the study period. 
The total volume during the study period is 20 mL (10 mL x 2 times in total).

Collection of stool specimen:
You will be given a stool collection kit in advance and asked to submit it. (3 times in total)

Blood sampling for exploratory studies:
4ml per time Total during the study period is 12ml. (4ml x 3 times total)

Confirmation of medication status:
Check remaining medications and empty sheets to find out about medication status.

Investigation of concomitant medications:
We will review medications for complications and any new medications prescribed for complications or other treatments during participation in the study.

Investigation of remedies:
Check the use of relief medications (bisacodyl suppositories and prusseenide tablets).

Investigation of adverse events:
Check for any physical changes or discomfort.

questionnaire survey:
At the time of your visit, you will be asked to complete a questionnaire about the impact of constipation symptoms on your daily life.
Patient diary confirmation:
From the beginning of the observation period to the end of the treatment period, the following information will be recorded daily.

- Frequency of defecation, stool characteristics (BS score), presence of residual stool sensation, degree of straining
- Presence of defecation desire
- Whether or not the patient is taking any research medications
- Usage of remedies, etc.

Check for any omissions in the logbook when you come to the hospital.

- Exploratory Research

In this study, blood and stool samples will be collected for exploratory research. This blood and feces will be used to examine the effects of the increase in bile acids caused by the research drug on the intestinal microflora, etc.

The blood and stools are used to investigate the effects of the research drug on the intestinal microbiota. In the blood, bile acids, amino acids, etc. will be measured, and in the stool, intestinal microflora, bile acids, organic acids, amino acids, etc. will be measured.

In blood, bile acids, amino acids, etc. are measured.

Each sample (blood and stool) will be sent to the Department of Hepatobiliary and Pancreatic Gastroenterology, Yokohama City University.

A portion of the stool samples will be sent to the institution that measures intestinal microflora: Department of Pharmacology, Shimane University School of Medicine.

The stool sample will be sent to the institution that measures intestinal microflora: Department of Pharmacology, Shimane University School of Medicine.

Your sample will be replaced with an identification code (a combination of letters and numbers) to identify you, (anonymized), which will be replaced with an identification code (a combination of letters and numbers) to prevent identification of individuals.

The person to whom the sample should be sent and who is responsible is as follows.
The address and person in charge of sending your samples are as follows

Department of Gastroenterology and hepatology, Yokohama City University Responsible person: Takaomi Kessoku

Department of Pharmacology, Shimane University School of Medicine
3.8 Study duration and number of participants
Enrollment period: From the date of publication of the jRCT* (date notified by the Minister of Health, Labour and Welfare) to July 31, 2022.

Research period: From the date of publication of jRCT* (date of notification to the Minister of Health, Labour and Welfare) to November 30, 2023.

*This system is used for procedures such as application for accreditation and notification of changes to the Minister of Health, Labour and Welfare in accordance with the Clinical Research Act.
A total of 100 people are expected to participate in this study.

4. Name of the medical institution and the name and title of the principal investigator (in the case where the specified clinical research is conducted as a multicenter joint research, the name and title of the principal investigator and the name of other medical institutions, including the name and title of the principal investigator of such medical institutions).

4.1 Name of medical institution
Yokohama City university hospital

4.2 Name and title of principal investigator
Principal investigator: Takaomi Kessoku    Position: Clinical Lecturer

4.3 Name of the collaborating institution, name and title of the principal investigator(s) at the institution

<table>
<thead>
<tr>
<th>Name of medical institution</th>
<th>Name of Principal Investigator</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yokohama City university hospital</td>
<td>Takaomi Kessoku</td>
<td>Clinical Lecturer</td>
</tr>
<tr>
<td>Iwasaki Internal Medicine Clinic</td>
<td>Tomoyuki Iwasaki</td>
<td>Director</td>
</tr>
<tr>
<td>Kanagawa Dental College Yokohama Clinic</td>
<td>Takeo Kurihashi</td>
<td>Head of hospital department</td>
</tr>
<tr>
<td>International University of Health and Welfare, Atami Hospital</td>
<td>Takayuki Kato</td>
<td>Chief of Gastroenterology</td>
</tr>
<tr>
<td>Namiki Koiso Clinic</td>
<td>Machiko Nakatogawa</td>
<td>Doctor</td>
</tr>
</tbody>
</table>
5 Anticipated benefits and disadvantages of conducting specific clinical research

- **Anticipated profit**
  
  Although there is no direct benefit to participating in this study, we hope to be able to scientifically prove the efficacy of the study drug (trade name: Guufis tablets 5 mg) in chronic constipation when taken over time. However, if we can scientifically prove the efficacy of the study drug (product name: Gupfis 5mg) in the treatment of chronic constipation when taken over a long period of time, patients with the same disease may benefit. However, if we can scientifically prove the efficacy of the studied drug (brand name: Guphyth Tablets 5 mg) in chronic constipation when taken over a long period of time, patients with the same disease may benefit. It could lead to satisfaction with the treatment and also to improve the impact of the disease on their daily life.

- **Anticipated disadvantages**
  
  Elobixibat, the research drug, is already marketed in Japan as a medication to improve chronic constipation. The following side effects have been reported. The following adverse reactions have been reported to date.
  
  In clinical trials in Japan up to the time of approval, adverse reactions were observed in 292 of 631 patients (46.3%).
  
  The most common adverse reaction was abdominal pain (120%). The most common adverse reactions included abdominal pain in 120 patients (19.0%) and diarrhea in 99 patients (15.7%). Other adverse reactions, by frequency, were as follows.
The table lists various symptoms and their frequencies:

<table>
<thead>
<tr>
<th>Category</th>
<th>Over 5%</th>
<th>1 to less than 5</th>
<th>Less than 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Abnormal liver function tests (increased ALT (GPT), increased AST (GOT))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychoneuromotor system</td>
<td>Headache, floating dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulatory organ</td>
<td>a glow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digestive organs</td>
<td>Abdominal pain (19.0%), diarrhea (15.7%), Lower abdominal pain, Abdominal bloating</td>
<td>Nausea, epigastric pain, and abdominal discomfort, soft stools</td>
<td>Gastrointestinal problems, dysgeusia, dysuria, constipation Vomiting, abnormal gastrointestinal sounds, constipation, endostomia</td>
</tr>
<tr>
<td>Allergies</td>
<td>Urticaria, urticaria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>Increased eosinophil count, anemia</td>
<td>Increased vitamin E</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>CK (CPK) increase</td>
<td></td>
<td>dysmenorrhea</td>
</tr>
</tbody>
</table>

Side effects other than these symptoms may also occur. In order to respond quickly to side effects, we will carefully examine you to see what happens to your body. If you experience any unusual symptoms during the study period, please notify your physician so that appropriate action or treatment can be taken. If your physician determines that the study needs to be terminated due to worsening laboratory values or side effects during the study period, the study will be terminated immediately.

If we learn any new safety information other than what we have told you, we will inform you immediately and confirm whether or not we will continue the study.

In this study, you will be asked to discontinue the laxatives you have been using in your treatment from the observation period. You will be asked to use a relief medication instead. In addition, if you are assigned to a placebo, it will not be effective as a medication. In research, you may have more office visits and...
tests than in the general population, and it may take longer to see you. There are other medications and treatments that you should not use while participating in research. If you wish to use any of the following medications, treatments, or tests while participating in research, please consult your physician in advance.

【Medications that should not be used during the study】
<table>
<thead>
<tr>
<th>Type of medication</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid preparations (ursodeoxycholic acid, kenodeoxycholic acid, and Dehydrocholic acid)</td>
<td>From observation period to the end of the treatment period</td>
</tr>
<tr>
<td>Bile acid transporter inhibitors other than research drugs</td>
<td></td>
</tr>
<tr>
<td>Various laxatives (magnesium oxide preparations, sodium picosulfate, sennosides, etc.) Excluding relief drugs</td>
<td></td>
</tr>
<tr>
<td>Aluminum-containing antacids (sucralfate hydrate, aldioxan, etc.)</td>
<td></td>
</tr>
<tr>
<td>Cholestyramine, Cholestyramide</td>
<td></td>
</tr>
<tr>
<td>Kampo drugs indicated for constipation (Daewo Ganso Tang, Chogoshouki Tang, Daishibako Tang, etc.)</td>
<td>From observation period to the end of the treatment period</td>
</tr>
<tr>
<td>Drugs for irritable bowel syndrome (e.g., ramosetron hydrochloride, calcium polycarbophil, trimebutine maleate)</td>
<td></td>
</tr>
<tr>
<td>5-HT3 antiemetic</td>
<td></td>
</tr>
<tr>
<td>Gastroprokinetic agents (mosapride citrate, metoclopramide, domperidone, etc.)</td>
<td></td>
</tr>
<tr>
<td>Macrolide antibiotics (erythromycin, roxithromycin, azithromycin, etc.)</td>
<td></td>
</tr>
<tr>
<td>Antidepressants, antipsychotics, anxiolytics, tranquilizers *Except when used to treat insomnia</td>
<td></td>
</tr>
<tr>
<td>Anticholinergics (excluding topical application)</td>
<td></td>
</tr>
<tr>
<td>Supplements and other products designed to improve constipation</td>
<td></td>
</tr>
<tr>
<td>Intestinal cleanser</td>
<td></td>
</tr>
</tbody>
</table>

【Treatments and tests that are prohibited during the study period】
### Type of treatment

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enemas, bowel cleansing, and stool extraction</td>
<td>From the observation period to the end of the treatment period</td>
</tr>
<tr>
<td>Biofeedback and other constipation treatments</td>
<td></td>
</tr>
<tr>
<td>Lower gastrointestinal endoscopy</td>
<td></td>
</tr>
</tbody>
</table>

### [Medications that should be used with caution during the study]

<table>
<thead>
<tr>
<th>Type of medication</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropic agents (digoxin, tabigatran etexilate methanesulfonate)</td>
<td>During the treatment period</td>
</tr>
<tr>
<td>mitazolam</td>
<td></td>
</tr>
</tbody>
</table>

### 1 That refusal to participate in the specified clinical research is voluntary.

You are free to decide for yourself whether or not to participate in this study. You will not be disadvantaged in any way if you decline to participate.

### 5.1 Withdrawal of Consent

You may withdraw your consent at any time after you have agreed to participate in the research (even during the study period). However, if you decide to discontinue participation in the study after it has begun, you will be responsible for your health care after the discontinuation. However, if you decide to discontinue participation in the study after it has begun, you must follow the instructions of your physician regarding your health care after the discontinuation. If you decide to discontinue participation in the study after it has begun, please follow the instructions of your physician regarding your health care after the discontinuation.

### 5.2 The fact that no disadvantageous treatment will be suffered by refusing to participate in the specified clinical research or by withdrawing consent

You will not be disadvantaged if you do not consent to participate in this study or if you withdraw your consent during the course of the study after you have given your consent.

If you do not consent to participate in this study, or if you withdraw your consent during the course of the study, you will not be disadvantaged in any way. In such cases, we will provide you with the best possible treatment using the methods that have been used to date.

If you withdraw your consent for exploratory research samples (blood and stool) before they are measured and analyzed your samples will be disposed of after appropriate processing.

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However, if measurement and analysis have already been conducted at the time of your request for withdrawal of consent, or if the results of the study have been published in a journal or other publication, your samples will be disposed of after appropriate processing. If you have already been measured and analyzed, or if the results of the study have been published in a paper or other publication, it may not be possible to dispose of the results of the analysis obtained. The results of the analysis may not be disposed of.

6 Methods of Information Disclosure for Specified Clinical Research

In conducting research, matters that the World Health Organization requires to be made public and other matters that contribute to ensuring transparency in the process of clinical research and the public’s choice to participate in clinical research shall be recorded (registered) in a database maintained by the Ministry of Health, Labour and Welfare (“jRCT”). In conducting the research, we will disclose matters that the World Health Organization requires to be disclosed and other matters that contribute to ensuring the transparency of the clinical research process and the public’s choice to participate in clinical research by recording (registering) them in a database maintained by the Ministry of Health, Labor and Welfare (hereinafter referred to as “jRCT”: jRCT = Japan Registry of Clinical Trials). The results of this research will also be published in jRCT, but in this case, the personal information of the study participants will be kept confidential. The jRCT will be published in the following location. URL: https://jRCT.niih.go.jp/

6.1 A statement that the research protocol and other materials relating to the conduct of the Specified Clinical Research may be obtained or inspected at the request of the subject of the Specified Clinical Research or the subject’s representative, and the method of obtaining or inspecting such materials

If you wish, you may obtain or view the research protocol and materials on research methods related to the implementation of this research to the extent that it does not interfere with the protection of the personal information of other research subjects or the originality of the clinical research in question.

However, after you request access, you will be required to go through various procedures or to the principal investigator to ensure the protection of your personal information and the originality of the research as described above. However, after the request for access is made, various procedures or consultations with the principal investigator and the research organization will be conducted to ensure the protection of personal information and the
originality of the research as described above. As a result, it may take some time before the materials are presented. As a result, please understand that it may take some time before the materials are presented, or that only a portion of the requested materials may be presented. Please understand that it may take some time to present materials or that only some of the requested materials may be presented.

7 Matters related to the protection of personal information of subjects of the specified clinical research

Data related to this research, such as samples and medical information provided by you, will not be used to identify you personally. Name will be replaced with an identification code (a combination of letters and numbers) to prevent personal identification. The results of this research may be made public in academic or medical papers.

The results of this study may be published in academic conferences or medical papers, but only information that has been replaced with an identification code will be made public. However, only the information that has been replaced with the identification code will be published, thus protecting your privacy. The results of this research may be published in academic conferences or medical papers.

7.1 Methods of Storage and Disposal of Samples, etc.

Samples will be stored and managed by the Department of Hepatobiliary and Pancreatic Gastroenterology, Yokohama City University, and will be destroyed in anonymized form five years after completion of the study. Samples sent to the Department of Pharmacology, Shimane University School of Medicine will be discarded after measurement.

If consent is withdrawn, the anonymized numbers will be deleted and the samples will be disposed of appropriately. However, this does not apply if the measurement, analysis, and results of this study have already been published at the time of withdrawal of consent.

Paper data will be stored in a locked cabinet, and electronic data will be stored with a password in accordance with the security regulations at each facility. Data will be retained for five years after the study is completed to allow for later determination of the accuracy of the study. After the storage period, we will take the utmost care to ensure that personal and confidential information is not leaked. Paper media will be shredded or incinerated, and electronic media will be physically and electronically rendered unreadable before being destroyed.

7.2 If there is a possibility that the sample/information obtained from the
subject of the clinical research will be used for future research that is not specified at the time consent is obtained from the subject of the clinical research or will be provided to other research institutions, a statement to that effect and the details expected at the time consent is obtained.

In this research, the samples, medical information, and other research data provided by you may be used for other research in the future. In such cases, the research plan will be revised. In such a case, we will review and approve the research plan again before using the data. If you do not want us to use your data for this research, please contact us. If you do not want us to use your data, please let us know. If you do not want us to use your data, please let us know. However, if you do not want us to use your data during the research stage (e.g., after research data such as samples and medical information have been processed into a form that does not identify individuals), please let us know. However, please understand that we may not be able to respond to your request depending on the stage of the research (e.g., after research data such as samples and medical information have been processed into a form that does not identify individuals). Please understand that there is a possibility that we may not be able to respond to your request.

8 Statement that the materials pertaining to the clinical research may be inspected by an accredited clinical research review committee, the Ministry of Health, Labour and Welfare, etc. for monitoring, auditing, etc., and that in such cases, personal information will be used appropriately and that signing the consent document will constitute authorization for such inspection.

If you participate in this study, for the purpose of verifying that this study was conducted properly. If you participate in this research, your medical records, including your medical chart, may be viewed by a representative of the company contracted by the principal investigator, a representative of the Ministry of Health, Labor and Welfare, and a representative of the Clinical Research Review Committee. The Ministry of Health, Labour and Welfare and the Clinical Research Review Committee may inspect your medical records to ensure that the study was conducted properly. Those who inspect the records are legally obliged to keep them confidential. Your privacy will be protected because of the legal obligation of confidentiality.

Please note that by agreeing to participate in this study and signing the consent form, you are also consenting to this access. consent to this access as well.

9 Status of conflicts of interest with respect to the specified clinical research and the existence or nonexistence of involvement of the manufacturer or distributor of the drug, etc. in such clinical research as
specified in the Conflict of Interest Criteria and the details thereof.

In conducting clinical research, there may be situations in which a third party suspects that fair and proper judgment is being obstructed or impaired for the benefit of the company, or may be suspected by a third party to be impairing the fairness and appropriateness of judgment for the benefit of the company. Such a situation is called a "conflict of interest. A situation in which fair and proper judgment is obstructed may include interpreting data in a way that favors a particular company that has provided funds, etc., or tending to ignore data that is unfavorable to the company, or a tendency to ignore inconvenient data. In conducting or reporting research To ensure that professional judgment is not bent in favor of financial or other personal interests It is important to check for conflicts of interest in order to

This research will be funded and managed by EA Pharma, Inc. and Mochida Pharmaceuticals, Inc. which manufacture and market the research drug (Elobixibat; product name: Gufis Tablets 5 mg). The research drug will be provided free of charge by EA Pharma Co.

Conflict of interest management standards and conflict of interest management have been prepared in advance for this study, and the study has been reviewed and approved by an accredited clinical research review committee. The results of this study will not be influenced by the opinions of the funders or drug providers, and the results will be published in medical societies, papers, etc., regardless of whether they are favorable or unfavorable to the funders or drug providers.

10 System for handling complaints and inquiries
If you have any questions about this research, please do not hesitate to contact us at any time.
Consultation Desk]
Department of Hepatobiliary and Pancreatic Gastroenterology, Yokohama City University
Principal Investigator: Takaomi Yuzoku
TEL: 045 (787) 2640 (weekdays from 10:00 to 16:00)
Patient Support Center (2)
3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan
Yokohama City University Hospital
Phone number: 045-787-2800 (main) (weekdays: 9:00-17:00)

11 Matters related to costs associated with the implementation of specific
clinical research
For V2 through V5 and when the study is discontinued, the cost of medical examinations, tests, and drugs will be paid from the research fund. V1 will be treated by insurance as usual, and the co-payment will be made by the patient. Research drugs will be provided free of charge by EA Pharma Co. In addition, a QUO card worth 5,000 yen per visit will be given as a burden reduction expense when V2, V3, V4, and V5 are conducted.

12 Availability and details of other treatments and comparison with the anticipated benefits and disadvantages of other treatments
In addition to this medication, other medications such as Pulsenide tablets, Linzess, and Mobicol are available for the treatment of chronic constipation. If you do not wish to receive this medication, we will treat you with one of the other medications currently in use at this hospital that we believe is best for you.

13 Matters concerning compensation and provision of medical care for damage to health caused by the implementation of specified clinical research
If you suffer any health problems as a result of your participation in this research, your physician will provide appropriate treatment and other necessary measures. In such cases, treatment will be provided by insurance and you will be responsible for paying the co-paid medical expenses. In such cases, treatment will be provided by insurance and you will be responsible for paying your own medical expenses.
In the event that liability for compensation arises due to health damage caused by this research, or in the event that the patient dies or suffers from a permanent disability of level 1 or 2
In addition, we have clinical research liability insurance to cover compensation in the event of health damage resulting from this research, or in the event that a patient dies or suffers a level 1 or 2 residual disability. There are certain conditions for compensation. Payment of compensation may be excluded or limited if any of the following are identified
1) Significant deviations from the research protocol
2) If there is willful misconduct or negligence, or medical malpractice on the part of the principal investigator, subinvestigators, etc.
3) In the event of illegal acts or non-performance by a third party
4) In the case of intentional or gross negligence on the part of the patient, etc.
In the event of a health hazard, the name and contact information of the principal investigator or subinvestigator of the study, as listed in “17. If a health hazard occurs, please contact the Principal Investigator or the
Research Assigning Physician listed in "17 Name and Contact Information of Principal Investigator or Research Assigning Physician".

14 Matters to be reviewed by the Authorized Clinical Research Review Committee that performs review and opinion services for the Specified Clinical Research, complaints and contact points for inquiries of said committee, and other matters related to the Authorized Clinical Research Review Committee for said Specified Clinical Research.

Yokohama City University has established a Clinical Research Review Committee accredited by the Minister of Health, Labor and Welfare, which is composed of medical, pharmacological and other experts, as well as non-specialists and those who have no vested interest in Yokohama City University. The committee members are not experts or specialists in the field of pharmacology, etc., and have no interest in Yokohama City University.

Name of the Certified Clinical Research Review Committee: Yokohama City University Clinical Research Review Committee
Establisher of the Authorized Clinical Research Review Committee: Public University Corporation Yokohama City University
Location of the accredited clinical research review committee: 3-9 Fukuura, Kanazawa-ku, Yokohama City, Kanagawa Prefecture

Information on this Accredited Clinical Research Review Committee (procedure manual, committee roster, and summary of meeting records) is available to the public and can be freely viewed on the following website.
https://www.yokohama-u.ac.jp/amedrc/ethics/ethical/ycu_crb.html?channel=main
https://jcrb.nih.go.jp/

Complaints and inquiries about the committee
Yokohama City University Clinical Research Review Committee Secretariat
TEL: 045-370-7627

15 Other matters necessary for the implementation of specific clinical research
15.1 Conditions and reasons for discontinuation of participation in the clinical research

If you request to withdraw from participation in the study, we will discontinue. In addition, if any of the following apply to you if you do not meet the criteria for participation after enrollment, or if you are found to be unsuitable for the study due to violations of the criteria for non-participation.
1. after enrollment, it is found that you do not meet the criteria for participation or that you violate the criteria for non-participation and are not appropriate for the subject of the study. 2.

2. when it is difficult to continue the study due to worsening of symptoms or findings of the disease, or side effects, etc.

3. if pregnancy is detected; or 4. if the subject’s physician determines that the subject is pregnant; or

4. other cases in which the physician in charge determines that it is difficult to continue the research. Even after the research is terminated during the course of the study, your health condition may be followed up if the physician in charge deems it necessary. We may follow up on your health condition even after the research is terminated during the course of the study, if the doctor in charge deems it necessary. The data obtained up to that point will be used as valuable information for this research. If you withdraw your consent for the use of your data until the discontinuation of the study if you wish to withdraw your consent for the use of your data until the study is terminated, please let us know.

15.2 When information is obtained that may influence the subject’s or surrogate’s decision to continue participation in the clinical research, to promptly explain and reconfirm the subject’s or surrogate’s willingness to continue participation

When information on efficacy or safety that may affect your consent is obtained after the start of the research, or when changes are made to the research plan that may affect your consent, the physician in charge will promptly provide you with this information and confirm with you whether or not you wish to continue participating in this research.

15.3 Treatment of Contingent Findings

Your physician should be informed of any findings from the tests performed in this study that are found to be suspicious of obvious abnormalities by chance. A detailed explanation can be given to you, your family or, if necessary, your referring physician.

15.4 Subjects of Clinical Research Must Observe

Please observe the following items as they are necessary to protect your health during the research and to collect accurate research data.

(1) If you visit another hospital, please inform that physician that you are participating in this study. Also, please inform your doctor that you have seen
another doctor. After receiving your permission, we may inquire about your medications and your symptoms with the physician at the other hospital.

(2) Please be sure to come to the hospital on the day of your scheduled visit. (If you are unable to make it, please let us know in advance.)

(3) If you are currently using any medications (including over-the-counter medications and health foods), or if you wish to use or stop using any medications after participating in the study, or if you wish to undergo any new tests or treatments other than medications, please consult your doctor in advance. (Medications may interact with each other, which means that when used together, they may have a negative effect on your health, either by losing their effectiveness or by having a stronger effect.)

(4) 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.

(5) On the day of your visit, please bring everything with you, including your patient diary, excess research medication, and empty research medication sheets.

(6) Women of childbearing potential should use contraception during participation in the study. If you believe that your contraception was not reliable, or if you become pregnant, please inform us immediately.

(7) Be sure to inform your doctor of any changes in your address, telephone number, or other contact information.

(8) If you decide to withdraw from participation in the study after starting this medication, either before or after taking this medication, please notify your doctor as soon as possible.

If you forget to take your medication or take two doses at once, you may not get the full effect of the medication or you may not get the full effect of the medication or too strong an effect, or you may increase the risk of unexpected side effects. Please be sure to follow these instructions. Please be sure to take your medication according to these instructions.

16 Name and contact information of principal investigator or subinvestigator

Principal Investigator: Takaomi Shigurashi
Affiliation: Department of Palliative Medicine
Phone: 045-787-2800 (main) (weekdays: 9:00-17:00)

* Please consult the above physician regarding the content of the research and any questions or concerns you may have regarding it.
Agreement

Dear Director of the Hospital, Yokohama City University Hospital

Title of the clinical trial: “A multicenter, randomized, double-blind, placebo-controlled, comparative study to evaluate the efficacy and safety of 12-week administration of AJG533 (elobixibat) in patients with chronic constipation.

☐ 1. Introduction
☐ 2. Name of the specific clinical research to be conducted, the fact that the administrator of the medical institution where the specific clinical research is to be conducted has given his/her approval, and the fact that the implementation plan has been submitted to the Minister of Health, Labour and Welfare.
2. The name of the specified clinical research to be conducted, the approval of the administrator of the medical institution in charge of conducting the specified clinical research, and the submission of the implementation plan to the Minister of Health, Labor and Welfare.
☐ 3. Method and duration of the clinical research Reason for selection as a subject of the specified clinical research
☐ 4. Name of the medical institution and the name and title of the principal investigator
☐ 5. Anticipated benefits and disadvantages of the specified clinical research
☐ 6. Statement that refusal to participate in the specified clinical research is voluntary, matters concerning withdrawal of consent, and matters concerning the disadvantages of refusing to participate in the specified clinical research or withdrawing consent, that no one will be treated disadvantageously for refusing to participate in the specified clinical research or for withdrawing consent.
☐ 7. Methods of disclosing information on the Specified Clinical Research, and the availability of research protocols and other materials on the implementation of the Specified Clinical Research upon request of the subjects of the Specified Clinical Research, etc. 7. The method of information disclosure concerning the specified clinical research, the fact that the research protocol and other materials concerning the implementation of the specified clinical research may be obtained or inspected at the request of the subjects of the specified clinical research and the method of obtaining or inspecting such materials
☐ 8. Matters concerning the protection of the personal information of the subjects of the Specified Clinical Research Methods of storage and disposal of samples, etc.
Methods for storing and disposing of samples and information obtained from subjects of clinical research that can be used for future research that will not be specified at the time consent is obtained from the subject of the clinical research. If there is a possibility that the samples and information obtained from the subject of the clinical research will be used for future research or provided to other research institutions, a statement to that effect and the details assumed at the time the consent is obtained. If there is a possibility that the sample and information will be used for future research or provided to other research institutions that is not specified at the time consent is obtained from the subject of the clinical research, a statement to that effect and details of the assumptions made at the time consent is obtained.
☐ 9. Whether the materials related to the clinical research may be inspected by an accredited clinical research review committee, the Ministry of Health, Labour and Welfare, etc. in the course of monitoring, auditing, etc. and if so, what personal information will be disclosed in such inspection. 9. The fact that the materials related to the clinical research may be inspected by an accredited clinical research review committee, the Ministry of Health, Labour and Welfare, etc. during monitoring, audits, etc., and that personal information will be used appropriately in such cases, and that signing the consent document is an approval of such inspection
☐ 10. The status of conflicts of interest in the specified clinical research and the presence or absence of involvement in the clinical research by manufacturers and distributors of pharmaceuticals, etc., as specified in the conflict of interest criteria and the details of such involvement. 10. Status of conflicts of interest in the specified clinical research and existence or non-existence of involvement in the said clinical research by manufacturers, etc. of pharmaceuticals, etc. as defined in the conflict of interest criteria and the details thereof
☐ 11. System for responding to complaints and inquiries
☐ 12. Matters related to the cost of conducting the specified clinical research
☐ 13. Existence and details of other treatment methods and comparison with the expected benefits and
disadvantages of other treatment methods

14. Matters related to compensation and provision of medical care for health damage caused by the implementation of the specified clinical research

15. Matters to be examined by the Accredited Clinical Research Review Committee, which is in charge of reviewing and giving opinions on the Specified Clinical Research, and other matters concerning the Accredited Clinical Research Review Committee for the said Specified Clinical Research

16. Other matters necessary for the implementation of the Specified Clinical Research

17. Name and contact information of principal investigator or subinvestigator

I have received and fully understood the explanation of the above clinical trial from the physician in charge and agree to participate in this study of my own free will.

Patient’s Name

Date of Consent: Year Month Day

I acknowledge that the above items have been explained to me and that my consent has been obtained.

Explaining physician
Date of Explanation: Month/Day/Year

If you have any questions or concerns about the research in which you have agreed to participate, please contact the following:

Contact: Department of Palliative Medicine, Yokohama City University Hospital
Principal investigator: Takaomi Shigurashi
Telephone number: 045-787-2800 (switchboard)
Title of the clinical trial: “A multicenter, randomized, double-blind, placebo-controlled, comparative study to evaluate the efficacy and safety of 12-week administration of AJG533 (elobixibat) in patients with chronic constipation.

☐ 1. Introduction
☐ 2. Name of the specific clinical research to be conducted, the fact that the administrator of the medical institution where the specific clinical research is to be conducted has given his/her approval, and the fact that the implementation plan has been submitted to the Minister of Health, Labour and Welfare.

2. The name of the specified clinical research to be conducted, the approval of the administrator of the medical institution in charge of conducting the specified clinical research, and the submission of the implementation plan to the Minister of Health, Labor and Welfare.

☐ 3. Method and duration of the clinical research Reason for selection as a subject of the specified clinical research

☐ 4. Name of the medical institution and the name and title of the principal investigator

☐ 5. Anticipated benefits and disadvantages of the specified clinical research

☐ 6. Statement that refusal to participate in the specified clinical research is voluntary, matters concerning withdrawal of consent, and matters concerning the disadvantages of refusing to participate in the specified clinical research or withdrawing consent, that no one will be treated disadvantageously for refusing to participate in the specified clinical research or for withdrawing consent.

☐ 7. Methods of disclosing information on the Specified Clinical Research, and the availability of research protocols and other materials on the implementation of the Specified Clinical Research upon request of the subjects of the Specified Clinical Research, etc. 7. The method of information disclosure concerning the specified clinical research, the fact that the research protocol and other materials concerning the implementation of the specified clinical research may be obtained or inspected at the request of the subjects of the specified clinical research and the method of obtaining or inspecting such materials

☐ 8. Matters concerning the protection of the personal information of the subjects of the Specified Clinical Research Methods of storage and disposal of samples, etc.

Methods for storing and disposing of samples and information obtained from subjects of clinical research that can be used for future research that will not be specified at the time consent is obtained from the subject of the clinical research. If there is a possibility that the samples and information obtained from the subject of the clinical research will be used for future research or provided to other research institutions, a statement to that effect and the details assumed at the time the consent is obtained. If there is a possibility that the sample and information will be used for future research or provided to other research institutions that is not specified at the time consent is obtained from the subject of the clinical research, a statement to that effect and details of the assumptions made at the time consent is obtained

☐ 9. Whether the materials related to the clinical research may be inspected by an accredited clinical research review committee, the Ministry of Health, Labour and Welfare, etc. in the course of monitoring, auditing, etc. and if so, what personal information will be disclosed in such inspection.

9. The fact that the materials related to the clinical research may be inspected by an accredited clinical research review committee, the Ministry of Health, Labour and Welfare, etc. during monitoring, audits, etc., and that personal information will be used appropriately in such cases, and that signing the consent document is an approval of such inspection

☐ 10. The status of conflicts of interest in the specified clinical research and the presence or absence of involvement in the clinical research by manufacturers and distributors of pharmaceuticals, etc. as specified in the conflict of interest criteria and the details of such involvement. 10. Status of conflicts of interest in the specified clinical research and existence or non-existence of involvement in the said clinical research by manufacturers, etc. of pharmaceuticals, etc. as defined in the conflict of interest criteria and the details thereof

☐ 11. System for responding to complaints and inquiries

☐ 12. Matters related to the cost of conducting the specified clinical research

☐ 13. Existence and details of other treatment methods and comparison with the expected benefits and
disadvantages of other treatment methods

□ 14. Matters related to compensation and provision of medical care for health damage caused by the implementation of the specified clinical research

□ 15. Matters to be examined by the Accredited Clinical Research Review Committee, which is in charge of reviewing and giving opinions on the Specified Clinical Research, and other matters concerning the Accredited Clinical Research Review Committee for the said Specified Clinical Research

□ 16. Other matters necessary for the implementation of the Specified Clinical Research

□ 17. Name and contact information of principal investigator or subinvestigator

I have received and fully understood the explanation of the above clinical trial from the physician in charge and agree to participate in this study of my own free will.

Patient’s Name

Date of Consent: Year Month Day

I acknowledge that the above items have been explained to me and that my consent has been obtained.

Explaining physician

Date of Explanation: Month/Day/Year

If you have any questions or concerns about the research in which you have agreed to participate, please contact the following

Contact: Department of Palliative Medicine, Yokohama City University Hospital
Principal investigator: Takaomi Shigurashi
Telephone number: 045-787-2800 (switchboard)