Rationale and design of a multicentre, 12-week, randomised, double-blind, placebo-controlled, parallel-group, investigator-initiated trial to investigate the efficacy and safety of elobixibat for chronic constipation


ABSTRACT

Introduction Chronic constipation (CC) is a functional disorder that negatively impacts the quality of life of patients. This is a protocol for a multicentre, 12-week, randomised, double-blind, placebo-controlled study to test the efficacy and safety of elobixibat (EXB) versus placebo in patients with CC.

Methods and analysis This will be a multicentre, double-blind, placebo-control, randomised controlled trial. A total of 100 adult patients with CC, diagnosed based on Rome IV criteria, who fulfill the inclusion/exclusion criteria will be enrolled. The patients will be randomly assigned to receive EXB (10 mg) or placebo treatment (n=50 per group). Blood tests and stool sampling will be performed 12 weeks following initiation of treatment and questionnaires will be issued to participants. The primary outcome will be the change in complete spontaneous bowel movements after 12 weeks of administration. The secondary outcomes will include the change in Japanese Patient Assessment of Constipation Quality of Life and absolute serum and faecal bile acid.

Ethics and dissemination Ethics approval has been obtained from Yokohama City University Certified Institutional Review Board before participant enrolment. The results of this study will be submitted for publication in international peer-reviewed journals and the key findings will be presented at international scientific conferences.

INTRODUCTION

Chronic constipation (CC) is a frequently occurring functional disorder encountered in daily clinical practice, with a prevalence of 2 %-27% in Japan. It is more prevalent in women than in men, and the prevalence increases with age in both sexes. In addition, comorbid functional gastrointestinal diseases are common, and reduced quality of life (QOL) has also been reported. It is
important to establish a 12-week effective treatment for CC because of the high frequency of concomitant ischaemic heart disease among the patients and the poor prognosis of chronically constipated patients compared with that of non-constipated patients.

Elobixibat (EXB) is an oral drug for CC that specifically inhibits ileal bile acid transporter/apical sodium-dependent bile acid transporter (IBAT/ASBT) (a transporter involved in bile acid reabsorption) in the terminal ileum. EXB was approved for marketing in Japan in January 2018. EXB is able to inhibit IBAT, leading to inhibition of bile acid reabsorption and an increase in the amount of bile acid that reaches the large intestine; this promotes the secretion of water into the lumen of the large intestine, thereby improving gastrointestinal motility. A placebo (PBO)-controlled double-blind study confirmed that EXB improves various symptoms including the frequency of spontaneous bowel movements (SBMs), frequency of complete spontaneous bowel movements (CSBM), time to first SBM and stool consistency in Japanese patients with CC. However, the duration of treatment in the aforementioned trial was only 2 weeks, and it was a single-arm study with confirmed safety and efficacy for 52 weeks. In addition, there was no control group.

Recently, 12-week randomised controlled trials (RCTs) aimed at developing new drugs for CC have been conducted in Europe and the USA. In Japan, lubiprostone has been used as a comparator, and a clinical trial was conducted using the number of SBMs at 1 week as the primary endpoint. Safety was also assessed in a 52-week open study. Therefore, 12-week RCTs have not been conducted in Japan, and the efficacy and safety of the 12-week administration of EXB should be verified with a double-blinded comparison.

This study aims to investigate the efficacy and safety of the 12-week administration of EXB or PBO for 12 weeks in patients with CC.

METHODS AND ANALYSIS

Trial design

The Standard Protocol Items: Recommendations for Interventional Trials statement and checklist were followed in preparing the study protocol. The trial is designed as a multicentre, randomised, double-blind, PBO-controlled, parallel-group, investigator-initiated study to evaluate the efficacy and safety of EXB and PBO treatments. All treatments will be administered orally once daily to patients with CC for 12 weeks. The experimental groups will be as follows (figure 1): the EXB group (10 mg EXB) and the PBO group. The study plan involves recruiting 100 adult patients with CC from seven institutions (the Yokohama City University Hospital, International University of Health and Welfare Atami Hospital, Omori Red Cross Hospital, Yokohama Sakae Kyoai Hospital, Iwasaki Naika Clinic, Kanagawa Dental University Yokohama Clinical and Namiki Koiso-medi cal clinic) cohort. The study protocol and informed consent form are shown in online supplemental document 1. This trial was registered with ClinicalTrials.gov (number NCT04784780) on 28 February 2021. The trial results will be reported in conformity with the Consolidated Standards of Reporting Trials 2010 guidelines.

Rationale for treatment dose, mode and duration

A previous study used the primary endpoint of ‘SBM’, whereas this study will use ‘CSBM’, which represents the frequency of bowel movements assessed for QOL; this has been recommended by the European Medical Agency (EMA) guidelines in recent years. Previous studies had reported significant differences at week 2; however, CC is defined as unsatisfactory bowel movements for 3 months or longer. Therefore, efficacy after 2 weeks of administration does not necessarily indicate an improvement in CC. To demonstrate efficacy, the change in CSBMs after 12 weeks of administration has been set as our primary endpoint.

Drug supply

Only the Patient Enrolment Centre will be aware of the treatment allocation, and double-blinding of the physicians and patients will be maintained throughout until all patients have completed the 12-week study and the database with all study data has been locked. EXB tablets (5 mg) and the corresponding reference PBO, which are indistinguishable in appearance, are manufactured and supplied by EA Pharma Co. (Tokyo, Japan). For the
study drugs prescribed, the physicians will enter the drug allocation number provided by the Patient Enrolment Centre on the prescription form. The drug manager will dispense the study drug to the patient based on the drug allocation number.

Sample size estimation and interim analysis
The target enrolment number will be 50 patients per group, for a total of 100 patients. A previous phase 3 study showed that the change in CSBMs during week 2 of the observational period was 2.98±3.1 (mean±SD) in the EXB group (n=65) and 0.86±1.45 in the PBO-treated group (n=63).

Additionally, it was previously reported that the change in CSBMs at week 2 of the treatment period relative to week 2 of the observational period was calculated at 2.12 for the between-group difference and approximately 2.288 for the common-SD. Since the study period in this trial is longer than that of the previous study, it is assumed that the difference between the mean values of the groups will be small, whereas the variation in the difference between groups in the amount of change will be larger due to differences regarding the participating medical institutions in the previous study.

Therefore, in calculating the sample size for this study, it was assumed that the between-group differences and common-standard-deviations for the primary endpoint (CSBMs change relative to week 2 of the observational period at week 12 of the treatment period) will be 1.8 and 2.5, respectively. At this time, Student’s t-test provides a 2-sided significance level of 5% and a power of 90% for 43 patients per group.

Since the study period is longer than that of the previous study, a dropout rate of approximately 10% was assumed, and a total of 100 patients (50 per group) was selected to ensure adequate power.

Eligibility
The physicians will enter legally capable patients into the Screening List, assign an identification code to each patient, and determine eligibility according to the inclusion and exclusion criteria (table 1). If no eligibility issues are identified, the investigator, subinvestigator or investigative staff will enter the necessary information into the Electronic Data Capture (EDC) system for enrolment. A patient enrolment number will then be assigned, and enrolment will be completed.

Randomisation, masking and keycode open
The patients will be randomised to each group (EXB and PBO) at a ratio of 1:1 using a computer-generated centrally administered procedure (permuted block method, no factor for stratification). The contract research organisation will create the list of study drug randomisation and link the appropriate study drug number. After the investigators confirm the eligibility of participants, the required information will be entered into the EDC system, and the drug number will be issued. Investigators and patients will be blinded to the details of the assignment to conceal the drug allocation number with the independent contract research organisation until the keycode is opened. All trial drugs will be packed identically and identified only by the number assigned. As noted above, the treatment assignments will be fully masked from the patients and physicians.

Keycode break
If the investigator or subinvestigator considers it urgently necessary to break the study keycode prematurely, they will contact the individual responsible for the study drug randomisation to file the request. This may occur due to a serious adverse event (SAE), the need to treat an adverse event (AE) or other similar situations.

Adverse reactions and AE monitoring
AEs are defined as any unfavourable or unintended sign (including laboratory parameters and abnormal vital signs), symptom or disease that may occur during the study period. AEs that are not directly related to the study drugs may develop. The investigator or subinvestigator will assess the severity of the AEs. Any AE that fulfills any of the following criteria will be considered an SAE: death, life-threatening situation, requirement for hospitalisation or prolonged hospitalisation for treatment, disability, threat of disability, other serious conditions, congenital disease or anomaly in offspring. If an SAE occurs, the investigator or subinvestigator will treat it appropriately, and the investigator will immediately report the details to the Hospital Director, Minister of Health, Labour and Welfare and the study drug supplier.

Study procedures
The investigator or subinvestigator will perform all observations, tests, investigations and evaluations according to the descriptions provided in table 2. After the initiation of treatment, drug returns and blood test results will be evaluated to monitor for adherence at each visit. Blood/soil samples will be collected and stored to assess the gut microbiota, bile acid, short-chain fatty acids and amino acids. When the study drug is distributed to the participants at each visit, the pharmacist will provide instructions on the dosage and administration. The pharmacist will request that participants return the unused study drug at their next visit and record the number of tablets (packages) that are returned. These strategies will improve adherence to the intervention protocol.

Concomitant treatment
The administration of the following medications and therapy is prohibited from the start of the observational period to the end of treatment: various laxatives (magnesium oxide preparations, sodium picosulfate, sennoside, etc), bile acid transporter inhibitors other than the study drugs, Chinese herbal medicines with indications for constipation (Daio-kanzoto, Dai-kanzo-to, Dai-ko-to, Dai-saiko-to, etc), irritable bowel syndrome medications, 5-HT3 antiemetics, macrolide antibiotics, antidepressants
Table 1  Patient inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of registration</td>
<td>1. Patients with or suspected of having structural constipation</td>
</tr>
<tr>
<td>Patients who meet all of the following criteria (1–6)</td>
<td>2. Patients with or suspected of having functional ileus</td>
</tr>
<tr>
<td>1. Individuals diagnosed with chronic constipation according to the Rome IV criteria for chronic constipation</td>
<td>3. Patients with or suspected of having an inguinal hernia</td>
</tr>
<tr>
<td>2. Age: 20–85 years (at the time of informed consent)</td>
<td>4. Patients who have undergone laparotomy within 12 weeks before providing informed consent (excluding appendicitis resection)</td>
</tr>
<tr>
<td>3. Sex: any</td>
<td>5. Patients with a history of surgical or endoscopic procedures related to cholecystectomy and papillotomy</td>
</tr>
<tr>
<td>4. Outpatient</td>
<td>6. Patients with concomitant malignancies. However, patients who have undergone radical surgery or who have completed chemotherapy or radiotherapy can be enrolled.</td>
</tr>
<tr>
<td>5. Patients from whom written informed consent can be obtained</td>
<td>7. Pregnant women, breastfeeding women, women who are currently possibly pregnant, or patients who do not consent to contraceptive use during study participation</td>
</tr>
<tr>
<td>6. Patients who can record bowel movements in a patient diary</td>
<td>8. Patients with serious concomitant renal, hepatic or cardiac disease</td>
</tr>
<tr>
<td>9. Patients allergic to the study drug</td>
<td>10. Patients who meet contraindications for rescue medications (bisacodyl suppositories and Pursennid tablets). However, if either rescue drug is not contraindicated, registration is permitted.</td>
</tr>
<tr>
<td>11. Patients participating in other clinical studies within 4 weeks before providing informed consent, excluding observational studies</td>
<td>12. Other patients whose inclusion in the study is deemed inappropriate by the investigator or subinvestigator</td>
</tr>
</tbody>
</table>

At the time of allocation (baseline)

Patients who fulfil all of the following criteria (1–3)

1. Patients with ≤6 spontaneous bowel movements (SBMs)* during the 2-week observational period prior to the initiation of treatment.

2. Patients who did not have loose or watery stools (Bristol Stool Form Scale 6 or 7) in SBMs** during the 2-week observational period prior to the start of treatment.

3. Patients who do not use concomitant drugs or therapies during the observation period.

* Bowel movements occurring without laxatives/enemas or disimpaction. ** If laxatives or relief medications were used on the day before the start of the run-in period, bowel movements within one day after use will not be considered spontaneous.

SBMs, spontaneous bowel movements.

and anticholinergics, among others. The restricted concomitant medications are permitted only if the rescue medication prescribed for this study (bisacodyl suppository 10 mg/1 tablet once and Pursennid tablet 12 mg/2 tablets once) could only be used if defaecation is not observed for more than 2 consecutive days.

Criteria and procedure for withdrawal from the study

The investigator or subinvestigator will discontinue the enrolment of a patient in the study if they fulfil any of the following criteria: (1) the patient desires withdrawal; (2) the patient is found not to meet the inclusion criteria or to meet the exclusion criteria after enrolment; (3) if it is the opinion of the investigator or subinvestigator that having the patient continue in the study is inappropriate due to an AE; or (4) if the investigator or subinvestigator believes that having the patient continue in the study is not appropriate due to any other reason.

Criteria for reducing and increasing the dosage of medications

No criteria for reduction and escalation of the dose of EXB will be established in this study.
Table 2  Schedule of observations, tests and assessments

<table>
<thead>
<tr>
<th>Study week</th>
<th>V1</th>
<th>V2/randomisation</th>
<th>V3</th>
<th>V4</th>
<th>V5/EOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit window</td>
<td>Informed consent</td>
<td>Registration</td>
<td>Randomisation</td>
<td>Week 4</td>
<td>Week 8</td>
</tr>
<tr>
<td>Registration</td>
<td>-</td>
<td>2-4 weeks after registration</td>
<td>±7 days</td>
<td>±7 days</td>
<td>±7 days</td>
</tr>
</tbody>
</table>

- Informed consent ○
- Inclusion/exclusion criteria ○
- Demographics ○
- Vital signs/height and weight* ○ ○ ○ ○ ○
- Blood test ○ ○
- Registration ○
- Confirmation of administration start criteria/allocation ●
- Blood and stool collection for exploratory research ● ● ●
- Providing drugs ○ ○ ○
- Checking the medication status ○ ○ ○ ○
- Review concomitant medications ○ ○ ○ ○ ○
- Review rescue drugs ○ ○ ○ ○
- Review adverse events
- Questionnaire/ review patient diary† ○ ○ ○
- Patient diary confirmation

○ To be performed.
● After confirming the treatment initiation criteria, the drugs will be allocated.
◎ Test stool collection kits will be provided mandatorily at the previous visit.
*The patient’s vital signs, including blood pressure and pulse rate, will be recorded. Height and weight will be measured only at enrolment.
†Patient diaries will be provided on V1, and diary entries will be checked at each visit.

### Evaluation of efficacy

The primary efficacy endpoint will be the change in the number of CSBMs at week 12 of the treatment period compared with those at week 2 of the observational period, from the baseline to 12 weeks after treatment initiation. CSBMs are defined as the number of defaecations not induced by rescue medication and not accompanied by a sense of incomplete evacuation. CSBMs will be evaluated by having patients note each bowel movement in their diary. The secondary endpoints are provided in table 3. According to the EMA guidelines, the number of CSBMs, the responder ratio of CSBMs, Japanese Patient Assessment of Constipation Quality of Life (JPAC-QOL) score, and the desire to defaecate will be assessed in this study to evaluate not only bowel movements but also defaecation-specific QOL.

### Safety assessments

The following safety evaluations will be performed during each patient visit from week 2 of the observational period until the week 12 treatment period: incidence of AEs in the EXB group compared with that of the PBO group.
Table 3  Study endpoints

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Efficacy endpoints</th>
<th>Secondary endpoints</th>
<th>Safety endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>► Change in the number of complete spontaneous bowel movements* (CSBMs) at week 12 of the treatment period relative to week 2 of the observational period</td>
<td>► Change in the number of CSBMs* at weeks 1 through 11 of the treatment period relative to week 2 of the observational period</td>
<td>► Incidence of adverse events</td>
<td></td>
</tr>
<tr>
<td>► Change in the number of SBMs for each week of the treatment period relative to week 2 of the observational period</td>
<td>► Change in the number of SBMs at weeks 1 through 11 of the treatment period relative to week 2 of the observational period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>► Percentage of responders † as seen in the number of SBMs and the number of CSBMs observed in each week of the treatment phase</td>
<td>► Percentage of responders ‡ as seen in the number of CSBMs during treatment (12 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>► Percentage change in stool consistency based on the Bristol Stool Form Scale at each week of the treatment period relative to week 2 of the observational period</td>
<td>► Percentage change in the presence or absence of a sense of incomplete evacuation at each week of the treatment period relative to week 2 of the observational period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>► Percentage change in the degree of straining at each week of the treatment period relative to week 2 of the observational period</td>
<td>► Percentage change in the presence or absence of defecation desire at each week of the treatment period relative to week 2 of the observational period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>► Percentage change in the presence or absence of defecation desire at each week of the treatment period relative to week 2 of the observational period</td>
<td>► Change in JPAC-QOL scores at week 4 and week 12 relative to baseline (V2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>► Changes in the following at week 4 and week 12 relative to baseline (V2) 1. Changes in the absolute faecal gut microbiota and percentages 2. Changes in the absolute values and percentages of blood and faecal bile acid 3. Changes in the absolute values and percentages of faecal organic acids 4. Changes in the absolute values and percentages of blood and faecal amino acids 5. Changes in blood C4</td>
<td>► Changes in the presence or absence of defecation desire at each week of the treatment period relative to week 2 of the observational period</td>
<td></td>
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</tr>
</tbody>
</table>

All objectives will be compared between EXB 10 mg and placebo groups. C4, 7α-Hydroxy-4-cholesten-3-one.

*SMBs without a sense of incomplete evacuation.

†Responders are defined as subjects whose SBMs and CSBMs per week have increased by at least one relative to week 2 of the observational period, and a total of at least three times per week.

‡ Responder definition: at least three CSBMs per week and at least one CSBMs per week relative to baseline in 9 weeks of the entire treatment period (12 weeks), including at least 3 weeks during weeks 9–12 of the treatment period.

CSBMs, complete spontaneous bowel movements; JPAC-QOL, Japanese version of the patient assessment of constipation quality of life; SBMs, spontaneous bowel movements.

Analysis population

The set of participants to be analysed will be determined before locking the data of each patient and will be defined as follows. The modified intention-to-treat analysis, which is the full analysis set (FAS), and per-protocol set (PPS) will be used for the assessment of primary efficacy. The FAS will include all patients who are randomised, except those who meet any of the following criteria: (1) patients with serious violations of selection and exclusion criteria, (2) patients who have not received any dose of the study drugs and (3) patients who have no measurement of the efficacy.
endpoint. A PPS will include patients without protocol deviations. The FAS will be the primary analysis set for efficacy. For the assessment of secondary efficacy, the FAS will be used. The safety analysis set (SAS) will be used for safety assessment and will include all patients who receive at least one dose of the study drug.

**Statistical analysis**

The multiplicity of endpoints will not be accounted for in the analysis. The significance between the active drug and PBO for the primary endpoint will be based on analysis of covariance (ANCOVA) using the baseline (week 2 of the observational period) value as the covariate. For the analysis of secondary endpoints, the change in the number of CSBMs and SBMs, and JPAC-QOL in the treatment groups at weeks 1–11 of the treatment period relative to week 2 of the observational period will be compared and analysed by ANCOVA using the baseline value. The changes in stool consistency using the Bristol Stool Form Scale (BSFS) score and degree of straining will be analysed using the Wilcoxon rank-sum test. We will use Fisher’s exact test for comparison of the proportion of patients in the SBM and CSBM responder analyses and the proportion of patients with incomplete evacuation and loss of defaecation desire (LODD). Gut-microbiota, bile acid, organic acids and amino acids will be analysed using Student’s t-test, while taking into account the false discovery rate in the EXB and PBO groups using the Benjamini-Hochberg method. We will assess the statistical difference in C4 concentrations between the groups in the 2-week study using Student’s t-test.

The numbers and proportions of patients with adverse drug reactions will be summarised according to treatment group. All reported p values will be based on 2-sided tests and the significance level set at 0.05.

Statistical analyses will be performed using SAS, V.9.4 (SAS Institute).

**Interim analysis**

Not applicable.

**Data management, central monitoring and audit**

The investigators’ sites will maintain individual records of each patient as source data, including a copy of the patient’s written informed consent, medical records, laboratory data and other records or notes. All data will be collected by the independent data management centre. The data management centre will oversee the inter-study data sharing process. The clinical data entry, data management and central monitoring will be performed using the electric data capture VIEDOC 4 (PCG Solutions, Uppsala, Sweden). Furthermore, auditing will be planned and conducted by an external clinical research organisation.

**Study flow and schedule of enrolment, interventions and assessments**

A study flowchart is shown in figure 1. The study schedule is presented in table 2.

**Patient and public involvement**

In this RCT, patients will be involved in the recruitment and conduct of the study. The development of the research question and outcome measures will be based on patients’ priorities, experience and preferences. The burden of intervention will be assessed by patients before commencement of the trial; patients’ satisfaction with the treatment will be recorded as a part of the postintervention assessment.

**ETHICS AND DISSEMINATION**

The study protocol complies with the Declaration of Helsinki and the Ethics Guidelines for Clinical Trial Act published by the Ministry of Health, Labor, and Welfare, Japan. We obtained approval for this study from the Yokohama City University Certified Institutional Review Board on 4 February 2021 (CRB20-023, study protocol; Online supplemental document 1). The protocol and informed consent form were approved by the Yokohama City University Certified Institutional Review Board. Written informed consent for participation in the study will be obtained from all participating patients. The results of this study will be disseminated by face to face to participants who indicate interest in obtaining the results. The results of this study will be submitted for publication in international peer-reviewed journals and the key findings will be presented at international scientific conferences.

**DISCUSSION**

This is the first study proposed to explore the 12-week effect of EXB in patients with CC, focused on bowel movements and defaecation-related QOL with CSBMs as the primary endpoint.

In Japan, it is common to administer laxative pharmacotherapy for CC when symptoms do not improve sufficiently even after patients have received diet, lifestyle and defaecation habit guidance. Two types of conventional laxatives, magnesium oxide (MgO) and stimulant laxatives, are widely used in clinical practice; MgO is the most commonly prescribed drug. Regular monitoring of serum magnesium levels is necessary if MgO is prescribed to patients with renal impairment, such as older individuals and patients with chronic kidney disease. Stimulant laxatives exhibit potent effects, but there are concerns about dependence and drug tolerance due to continuous use, and in principle, they should be used only occasionally. Therefore, MgO, the dosage of which can be finely adjusted and has demonstrated safety, is often chosen as a first-line drug. However, because there is a risk of hyper-magnesaemia occurring not only in patients with renal impairment, as explained previously, but rarely in those with normal renal function, it is recommended that serum magnesium levels be monitored at 3–6 month intervals during 12-week high-dose administration of MgO.15

While stimulant laxatives are generally divided into two groups, anthraquinones (senna and rhubarb) and
diphenolics (bisacodyl, sodium picosulfate, etc), to date, most reported RCTs have involved diphenolic laxatives. Some RCTs and systematic reviews from Western countries have confirmed the efficacy of bisacodyl and sodium picosulfate.16–18 In fact, a recent review has highly recommended bisacodyl, whose efficacy has been reported at a high level of evidence.19 Regarding clinical trials of MgO, the most frequently prescribed drug for the treatment of chronic idiopathic constipation in Japan, Mori et al is the only reported study demonstrating that MgO significantly improves bowel movement and QOL compared with PBO.20,21 Additionally, Morishita et al first conducted a randomised PBO-controlled comparative study involving PBO, MgO and senna over a period of 4 weeks, and demonstrated that senna and MgO significantly improved the frequency of bowel movements and QOL score and appear effective in the treatment of constipation.21 There is an RCT of conventional laxatives (MgO and stimulant laxatives) for 4 weeks in patients with CC,20 21 and a 12-week randomised PBO-controlled trial of linaclotide, a novel laxative.22 However, no clinical trial has evaluated constipation drug with a novel mechanism of action, such as EXB, for 12 weeks using CSBMs and defaecation-specific QOL as the primary endpoint.

A web-based questionnaire-based survey reported that patients with CC had a significantly higher rate of LODD than healthy adults, with about 60% of patients losing their defaecation desire (DD), leading to the decrease of defaecation QOL.23 Bile acids are expected to have a restorative effect on DD because they have an effect to lower the rectal sensory threshold, which is an objective index of DD.24,25 EXB inhibits IBAT/ASBT (a transporter involved in bile acid reabsorption) in the terminal ileum.26 The IBAT inhibitory action of EXB increases the amount of bile acid reaching the colon by inhibiting bile acid reabsorption, thereby promoting water secretion into the lumen of the large intestine and gastrointestinal motility. In addition, we will assess a recovery ratio of LODD in the secondary endpoint.

In recent years, CSBMs have attracted attention in clinical trials as an indicator of the efficacy of therapeutic agents for constipation.13 To increase CSBMs, which is SBMs accompanied by a sensation of complete evacuation, facilitating the passing of stool that is type IV on the BSFS is important. A recent study suggested that type IV stool form contributes significantly to the improvement of QOL compared with other stool forms.25 Reports have revealed that patients with CC generally have low QOL.26 Using Patient Assessment of Constipation QOL, this study examined constipation-related QOL before and after drug treatment. Therefore, our study uses the BSFS and JPAC-QOL to assess constipation-related QOL.

Our study has the following strengths: (1) assessment of CSBMs is the primary endpoint; (2) the 12-week duration; (3) BSFS and bowel movements related to defaecation-related QOL are also measured as secondary endpoints; and (4) the measurement of faecal bile acid, serum bile acid, C4, gut-microbiota, organic acids and amino acids. Nevertheless, our study also has the following limitations: (1) lack of comparison with other laxatives; and (2) a patient population of a single ethnicity.

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**Contributors** KT, T.Kessoku and AN conceived the study. T.Kessoku conducted the feasibility phase work. Recruitment of participants and follow-up will be performed by AV, KT, YK, A0, MI, T.Kobayashi, TY, NM, T.Kato, JA, GF, ES, TH, HC, KH, MY, Ti, TK, MN, AS and NK. Analysis and interpretation of data will be conducted by MT, SD, KA, YI and AN. MT, SO and KA will perform bioinformatic analysis. All authors have read and approved the final manuscript.

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**Competing interests** The authors declare that they have competing interests. This study is funded by EA Pharma and Mochida Pharma., which is the distributor of elobixibat in Japan.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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REFERENCES
12 European Medicines Agency. Guideline on the evaluation of medicinal products for the treatment of chronic constipation (including opioid-induced constipation) and for bowel cleansing, 2015.
A multicenter, randomized, double-blind, placebo-controlled trial of the efficacy and safety of the long-term administration of AJG533 (elobixibat) to patients with chronic constipation.

(№TANK-27)

Principal Investigator: Takaomi Kessoku
Department of Palliative Medicine
Yokohama City University Hospital
Ver 3.0
Prepared on June 15, 2021
### Confidentiality Agreement

This study protocol is confidential information and is provided to research representatives, research investigators, research sub-investigators, research collaborators, certified clinical research review boards, EA Pharma Co., Ltd., Mochida Pharmaceutical Co., Ltd., and other trial professionals. This study protocol cannot be disclosed to any third party or used for purposes other than this study without the investigator's written consent, except when explaining the details of this study to subjects.

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<td>Ver 3.0</td>
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<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>CSBM</td>
<td>Complete Spontaneous Bowel Movements</td>
</tr>
<tr>
<td>CK</td>
<td>Creatine kinase</td>
</tr>
<tr>
<td>Cl</td>
<td>Chlorine</td>
</tr>
<tr>
<td>EOT</td>
<td>End of treatment</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic data capture</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case report form</td>
</tr>
<tr>
<td>FAS</td>
<td>Full analysis set</td>
</tr>
<tr>
<td>5-HT₃</td>
<td>5-Hydroxytryptamine type3 receptor</td>
</tr>
<tr>
<td>γ-GTP</td>
<td>Gamma-glutamyl transpeptidase</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>IBAT/ASBT</td>
<td>Ileal bile acid transporter/ apical sodium-dependent bile acid transporter</td>
</tr>
<tr>
<td>PAC-QOL</td>
<td>Patient assessment of constipation quality of life</td>
</tr>
<tr>
<td>K</td>
<td>Potassium</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>Na</td>
<td>Sodium</td>
</tr>
<tr>
<td>PPS</td>
<td>Per Protocol Set of Subject</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RomeIV</td>
<td>—</td>
</tr>
<tr>
<td>SBM</td>
<td>Spontaneous Bowel Movements</td>
</tr>
<tr>
<td>SAS</td>
<td>Safety Analysis Set of Subject</td>
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0. An Overview

<table>
<thead>
<tr>
<th>Study title</th>
<th>A multicenter, randomized, double-blind, placebo-controlled trial on the efficacy and safety of the long-term administration of AJG533 (elobixibat) to patients with chronic constipation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of the study drug</td>
<td>AJG533 (Elobixibat)</td>
</tr>
<tr>
<td>Target disease</td>
<td>Chronic constipation</td>
</tr>
<tr>
<td>Research methods, Study Design</td>
<td>Multicenter, randomized, placebo-controlled, double-blind trial</td>
</tr>
</tbody>
</table>

| Study period | Enrollment time: From the date of jRCT publication (MHLW Notification) to July 31, 2022  
Study period: From the date of jRCT publication (MHLW notification) to November 30, 2023 (approximately three years)  
Expected duration of participation by subjects: Up to 17 weeks after obtaining informed consent  
Observation period: two to four weeks  
Treatment period: 12 weeks (up to 13 weeks) |
<table>
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<tbody>
<tr>
<td>Study Protocol No.</td>
<td>TANK-27</td>
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<tr>
<td>Purpose</td>
<td>To investigate the superiority and safety of 10 mg AJG533 (elobixibat) administered orally once daily prior to a meal for 12 weeks over a placebo in subjects with chronic constipation via a double-blind controlled trial with a primary endpoint of change in the number of complete spontaneous bowel movements (CSBMs) at Week 12 of the treatment period relative to Week 2 of the run-in period.</td>
</tr>
</tbody>
</table>

| Target number of test subjects | Number of patients included in the analysis: 100 |

| Inclusion criteria | Selection criteria  
Patients who meet all of the following criteria (1–6)  
- **Time of registration**  
1. Individuals diagnosed with chronic constipation according to the Rome IV criteria for chronic constipation  
2. Age: 20–85 years (at the time of informed consent)  
3. Sex: Any  
4. Outpatient  
5. Patients from whom written informed consent can be obtained  
6. Patients who can record bowel movements in a patient diary  
- **At the time of allocation (baseline)** |

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BMJ Open 2022; 12:e060704. doi: 10.1136/bmjopen-2021-060704

Patients who meet all of the following criteria (1–3)

1. Patients with ≤6 spontaneous bowel movements (SBMs)* during the 2-week run-in period prior to the initiation of treatment.

*bowel movements occurring without laxatives/enemas or disimpaction.

In this study, if laxatives or relief medications were used on the day before the start of the run-in period, bowel movements within one day after use will not be considered spontaneous.

2. Patients who did not have loose or watery stools (Bristol Stool Form Scale 6 or 7) in SBMs* during the 2-week run-in period prior to the start of treatment.

*If laxatives or relief medications were used on the day before the start of the run-in period, bowel movements within one day after use will not be considered spontaneous.

3. Patients who do not use concomitant drugs or therapies during the observation period.

Exclusion criteria

Patients who satisfy any of the following criteria will be excluded.

1. Patients with or suspected of having organic constipation

2. Patients with or suspected of having functional ileus

3. Patients with or suspected of having an inguinal hernia

4. Patients who underwent laparotomy within 12 weeks before obtaining informed consent (excluding appendicitis resection)

5. Patients with a history of surgical or endoscopic procedures related to cholecystectomy and papillotomy

6. Patients with concomitant malignancies

   However, patients who have undergone radical surgery or who have completed chemotherapy or radiotherapy can be enrolled.

7. Pregnant women, breastfeeding women, women who are currently possibly pregnant, or patients who do not consent to contraceptive use during study participation

8. Patients with serious concomitant renal, hepatic, or cardiac disease
9. Patients allergic to the study drug
10. Patients who meet contraindications for rescue medications (bisacodyl suppositories and Pursennid tablets) However, if either rescue drug is not contraindicated, registration is permitted.
11. Patients participating in other clinical studies within four weeks before obtaining informed consent, excluding observational studies
12. Other patients whose inclusion in the study is deemed inappropriate by the investigator or sub-investigator

<table>
<thead>
<tr>
<th>NAME AND DOSE OF STUDY DRUGS</th>
<th>AJG533 (elobixibat) placebo-treated group</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJG533 (elobixibat) 10 mg group</td>
<td></td>
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<table>
<thead>
<tr>
<th>Method of administration, observation, and duration of administration</th>
<th>The study consists of a 2-week observation period and a 12-week treatment period. Study drugs are administered orally once daily before meals for 12 weeks during the treatment phase.</th>
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<th>Evaluation Items</th>
<th>Efficacy</th>
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<tr>
<td></td>
<td>Primary endpoint:</td>
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<tr>
<td></td>
<td>- Change in the number of complete spontaneous bowel movements* (CSBMs) at Week 12 of the treatment period relative to Week 2 of the run-in period</td>
</tr>
<tr>
<td></td>
<td>*SBMs without feeling of residual stool</td>
</tr>
<tr>
<td></td>
<td>Secondary endpoints:</td>
</tr>
<tr>
<td></td>
<td>- Change in the number of CSBMs* at Weeks 1 through 11 of the treatment period relative to Week 2 of the run-in period</td>
</tr>
<tr>
<td></td>
<td>- Change in the number of SBMs for each week of the treatment period relative to Week 2 of the run-in period</td>
</tr>
<tr>
<td></td>
<td>- Percentage of responders ** as seen in the number of SBMs and the number of CSBMs observed in each week of the treatment phase</td>
</tr>
<tr>
<td></td>
<td>**Responders are defined as subjects whose SBMs and CSBMs per week have increased by at least one relative to Week 2 of the run-in period, and a total of at least three times per week.</td>
</tr>
<tr>
<td></td>
<td>- Percentage of responders * as seen in the number of CSBMs during treatment (12 weeks)</td>
</tr>
</tbody>
</table>
**Responder Definition**: at least three CSBM per week and at least one CSBM per week relative to baseline in nine weeks out of the whole treatment period (12 weeks), including at least three weeks during Weeks 9-12 of the treatment period.

- Percentage change in stool consistency based on the Bristol Stool Properties Scale each week of the treatment period relative to Week 2 of the run-in period
- Percentage change in the presence or absence of residual stool at each week of the treatment period relative to Week 2 of the run-in period
- Percentage change in the degree of straining each week of the treatment period relative to Week 2 of the run-in period
- Percentage change in the presence or absence of the urge to defecate each week of the treatment period relative to Week 2 of the run-in period
- Change in JPAC-QOL scores at Week 4 and Week 12 relative to baseline (V2)
- Changes in the following at Week 4 and Week 12 relative to baseline (V2)
  1. Changes in the absolute fecal gut microbiota and percentages
  2. Changes in the absolute values and percentages of blood and fecal bile acids
  3. Changes in the absolute values and percentages of fecal organic acids
  4. Changes in the absolute values and percentages of blood and fecal amino acids
  5. Changes in blood C4

### Safety

**Incidence of adverse events**

### Inquiries

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<th>Principal Investigator:</th>
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<tr>
<td>Takaomi Kessoku</td>
</tr>
<tr>
<td>Department of Palliative Medicine, Yokohama City University Hospital</td>
</tr>
<tr>
<td>TEL: 045-787-2800 (representative)</td>
</tr>
<tr>
<td>Research office: Yokohama City University Hospital</td>
</tr>
</tbody>
</table>
### Purpose of this study

To investigate the superiority and safety of 10 mg AJG533 (elobixibat) administered orally once daily prior to a meal for 12 weeks relative over a (AJG533) placebo in subjects with chronic constipation via a double-blind controlled trial with a primary endpoint of change in the number of complete spontaneous bowel movements (CSBMs) at Week 12 of the treatment period relative to Week 2 of the run-in period.

### 2. Background and the scientific rationale for the study design

Elobixibat is an oral chronic constipation drug that specifically inhibits ileal bile acid transporter/apical sodium-dependent bile acid transporter (IBAT/ASBT) (a transporter involved in bile acid reabsorption) in the terminal ileum [1]. Elobixibat was approved for marketing in Japan in January 2018. Elobixibat’s ability to inhibit IBAT leads to the inhibition of bile acid reabsorption and to an increase in the amount of bile acids that reach the large intestine; this promotes the secretion of water into the lumen of the large intestine, thereby improving gastrointestinal motility. A placebo-controlled double-blind study has confirmed that elobixibat improves various symptoms including the frequency of spontaneous bowel movements, frequency of complete spontaneous bowel movements, time to first spontaneous bowel movements (SBMs), and stool consistency in Japanese patients with chronic constipation. However, the duration of treatment therein was only 2 weeks, and it was a single-arm study with a confirmed safety and efficacy of 52 weeks but no control group [2].

Recently, long-term (12-week) randomized controlled trials have been conducted for the development of drugs for chronic constipation in Europe and the United States. In Japan, lubiprostone has been used as a reference, and a clinical trial was conducted using the number of SBMs at one week as the primary endpoint. Safety was also assessed in an open study for 52 weeks. Therefore, long-term randomized controlled trials have not been conducted in Japan, and the efficacy and safety of the long-term administration of elobixibat should be verified via a double-blinded comparison.
This study investigates the efficacy and safety of the long-term administration of elobixibat or placebo for 12 weeks in patients with chronic constipation.

2.1. Target disease

Chronic constipation is a frequently occurring functional disorder, encountered in daily clinical practice with a prevalence of 2–27% in Japan. It is more prevalent in women than in men, and the prevalence increases with age in both sexes [3]. In addition, comorbidity with other functional gastrointestinal diseases is common, and decreased QOL has also been reported [4-6]. It is important to establish a long-term effective treatment for chronic constipation because of the high frequency of concomitant ischemic heart disease among the patients [7] and the poor life prognosis of chronically constipated patients than non-constipated patients [8].

2.2. Standard treatment

2.2.1. History of standard treatments that have been implemented to date

It is common to administer laxative pharmacotherapy for chronic constipation when symptoms do not sufficiently improve even after patients have received dietary, lifestyle, and defecation habit guidance. Two types of laxatives, magnesium oxides and irritant laxatives, are widely used in clinical practice; magnesium oxides are the most commonly prescribed drugs. Regular monitoring of serum magnesium levels is necessary if magnesium oxides are prescribed to patients with renal impairment, such as the elderly and patients with chronic kidney disease.

Irritant laxatives have potent effects, but there are concerns about dependence and drug resistance due to continuous use, and in principle, they should be used only occasionally. Therefore, magnesium oxide, whose dosage can be finely adjusted and is demonstrably safe, is often chosen as a first-line drug. However, because there is a risk of hypermagnesemia occurring not only in patients with renal impairment, as explained previously, but rarely in those with normal renal function, it is recommended that serum magnesium levels be monitored at 3- to 6-month intervals during long-term high-dose administration [9].

2.2.2. Current standard of care

Pharmacotherapy for chronic constipation is considered as standard treatment for the condition, alongside dietary guidance and lifestyle guidance.

However, as mentioned above, there are problems, such as side effects and tolerance/addiction, during long-term use of each first-choice drug [10-12].

In recent years, the number of drugs for the treatment of chronic constipation has increased, and high evidence-level formulations such as linaclotide and lubiprostone have emerged. In addition, Health and Medical Services documents [13, 14] from the Ministry of Health, Labor and Welfare
MHLW recommend the use of linaclotide, rubiprostone, elobixibat hydrate, macrogol 4000, and lactulose when the efficacy of the existing constipation drugs is insufficient, and the treatment status has changed significantly.

2.3. Treatment

The study drug elobixibat was approved for marketing in January 2018 for the treatment of chronic constipation (excluding constipation due to organic disease). The drug increases bile acid levels in the large intestine by inhibiting bile acid reabsorption transporters in the terminal ileum, promoting fluid and electrolyte secretion and further gastrointestinal motility. Since the drug is only minimally absorbed into the body and does not pass into the blood to become active, there are few concerns about drug interactions with concomitant medications.

Abdominal pain and diarrhea are the main treatment risks. In a domestic clinical study for chronic constipation, 292 (46.3%) of 631 patients had adverse reactions, including abnormal laboratory values, and the main adverse reactions were abdominal pain in 120 (19.0%) and diarrhea in 99 (15.7%).

The test treatment has been shown to improve patient satisfaction for constipation treatment based on complete spontaneous defecation by the 12th week of administration; this has been demonstrated for the first time in the country and abroad.

2.4. Study design and primary endpoints

This is a multicenter, randomized, placebo-controlled, double-blind trial in patients with chronic constipation.

[Primary endpoint] Change in the number of CSBMs during Week 12 of the treatment period relative to Week 2 of the run-in period

[Rationale]

In previous studies, the primary endpoint was set to "spontaneous bowel movements" (SBMs) [2], and EMA guidelines state that it is important to evaluate QOL [15]. Based on these findings, the primary endpoint of this study was set to "completely spontaneous bowel movements" (CSBMs), which associates bowel movements with QOL metrics. In previous studies, a significant difference was obtained after administration for two weeks, but chronicity in chronic constipation is defined as three months or more of unsatisfactory defecation [3]. Efficacy after two weeks of administration cannot be said to indicate improvement in the chronic aspect of chronic constipation; thus, to show the effectiveness of the study drug in chronic cases, we set our endpoint to the degree of change in CSBMs at Week 12 of treatment [16]. As for the placebo group, our criteria selected patients with less than three SBMs per week as well as patients in whom existing treatments were unsatisfactory.
Finally, we believe that the effect of switching from existing therapies to the study drug during the change from the run-in period to the treatment period will have no significant effect on patient safety.

2.5. Significance of this study

By setting SBMs without the feeling of residual stool (CBSMs) as the primary endpoint, demonstrating efficacy of the long-term administration of the study drug may provide patients with high satisfaction.

3. Study Drug Information

3.1. Study drug

- Names: AJG533 (Elobixibat)
- Brand name: Goofis® Tablets 5 mg
- Non-proprietary name: Elobixibat hydrate
- Storage conditions: Room temperature
- Manufacturing and sales company name: EA Pharma Co., Ltd.
- Indication: Chronic constipation (excluding constipation due to organic disease)
- Dosage and administration (method of use): AJG533 (elobixibat) 10 mg is orally administered once daily prior to meals. The dosage may be adjusted according to the symptoms. The maximum daily dose is 15 mg.
- Dosage form (appearance): pale yellow round film-coated tablet

3.2. Comparator

- Name: AJG533 placebo (elobixibat placebo)
- Generic name: -
- Manufacturing and sales company name: EA Pharma Co., Ltd.
- Indication: -
- Dosage and Administration (mode of use): AJG533 placebo (elobixibat placebo) is administered orally once daily prior to meals.
- Dosage form (appearance): Film-coated tablets whose appearance, odor, weight, etc. are indistinguishable from elobixibat hydrate tablets, and do not contain elobixibat.

3.3. Labeling

AJG533/AJG533 Placebo

Labeling of the drug box is shown in Figure 3.3.
3.4. Management of the study drugs

The study drugs will be provided to the principal investigators of each medical institution by EA Pharma Co., Ltd. Specific procedures for providing, storing, and managing the study drugs are specified separately in the “Procedures for the management of the study drugs”. The supervising physician will explain the details of the study to the study drug manager of the corresponding participating medical institution, submit the “Procedures for the management of the study drugs”, and request that these procedures be followed. During the research period, the study drug manager will store and manage the study drug appropriately, regardless of whether it will be used, and will prepare a study drug management table for recording the usage status of the study drug.

The supervising physician confirms the accuracy of the study drug management record, information on the leftover drug, and the contents of the case report; if any inconsistencies are found, the supervising physician immediately investigates the cause and makes any necessary corrections. After the study is completed, the supervising physician or the study drug manager reports information on all unused study drugs, etc. to the principal investigator and follows the instructions regarding disposal.

3.5. Ensuring the quality of the study drugs

In terms of the appropriate management of approved items, including pharmaceutical products, etc., the procedure for the management of the study drugs will be followed. If information indicating occurrences, such as poor quality of the study drug, is obtained from the research drug provider, the principal investigator will perform appropriate verifications and take necessary measures. The principal investigator will instruct the investigator of each medical institution about the necessary measures and report the measures taken to the research drug provider.

4. Criteria and definitions used in this study

- Diagnosis of chronic constipation uses the “Rome IV Diagnostic Criteria for Functional Constipation.”

- Characterization of stools is based on the Bristol Stool score (BS score).
For stool straining, a five-point evaluation is used: 1, no straining at all; 2, slight straining; 3, some straining; 4, strong straining; and 5, very strong straining.

The QOL assessment of chronic constipation uses the Japanese version of the Patient Assessment of Constipation Quality of Life (JPAC-QOL), a disease-specific scale.

5. Patient selection policy

5.1. Selection criteria

Patients who meet all of the following criteria (1–6)

At time of registration
1. Individuals diagnosed with chronic constipation according to the Rome IV criteria for chronic constipation
2. Age: 20 to 85 years (at the time of informed consent)
3. Sex: Any
4. Outpatient
5. Patients for whom written informed consent can be obtained
6. Patients who can record bowel movements in a patient diary

[Rationale]
1. Rome IV criteria, which are widely used internationally, were set as the diagnostic criteria for chronic constipation.
2. With respect to subjects’ voluntary participation in this study, the lower age limit for eligibility was set at 20 years, as this is the age at which individuals are legally able to provide informed consent. Further, for safety reasons, the upper age limit was set to 85 years.
3. Sex was not restricted to improve recruitment.
4. Stipulated because constipation is often treated in outpatient facilities.
5. Set in accordance with the spirit of the Declaration of Helsinki.
6. Set in order to correctly evaluate the efficacy of the study drug.

At the time of allocation (baseline)

Patients who meet all of the following 1. to 3. criteria:

1. Patients with ≤ 6 SBMs* during the 2-week run-in period prior to the initiation of treatment.
   *bowel movements occurring without laxatives/enemas or disimpaction. In this study, if laxatives or relief medications were used on the day before the start of the run-in period, bowel movements within one day after use will not be considered spontaneous.
2. Patients who did not have loose or watery stools (Bristol Stool Form Scale 6 or 7) in SBMs* during the 2-week run-in period prior to the start of treatment. *If laxatives or relief medications
were used on the day before the start of the run-in period, bowel movements within one day after use will not be considered spontaneous

3. Patients who do not use concomitant drugs or therapies during the observation period

[Rationale]

1. Set to uniformly select appropriate subjects.
2. and 2. Set to prevent inadvertent effects on the efficacy of the study drug.

5.2. Exclusion criteria

Patients satisfy any of the following conditions will be excluded:

- Time of registration
  1. Patients with or suspected of having organic constipation
  2. Patients with or suspected of having functional ileus
  3. Patients with or suspected of having an inguinal hernia
  4. Patients who underwent laparotomy within 12 weeks before obtaining informed consent (excluding appendicitis resection)
  5. Patients with a history of surgical or endoscopic procedures related to cholecystectomy and papillotomy
  6. Patients with concomitant malignancies
  7. However, patients who have undergone radical surgery or who have completed chemotherapy or radiotherapy can be enrolled.
  8. Pregnant women, breastfeeding women, women who are currently possibly pregnant, or patients who do not consent to contraceptive use during study participation
  9. Patients with serious concomitant renal, hepatic, or cardiac disease
  10. Patients with a history of allergy to the study drug.
  11. Patients who meet contraindications for rescue medications (bisacodyl suppositories and Pursenmid tablets). However, if either rescue drug is not contraindicated, registration is permitted.
  12. Patients participating in other clinical studies currently or within four weeks before obtaining informed consent, excluding observational studies. Other patients whose inclusion in the study is deemed inappropriate by the investigator or sub-investigator

[Rationale]

1. to 5. Set to prevent inadvertent effects on the efficacy of the study drug.
6. to 10. Set to ensure the safety of subjects.
11. Set for ethical reasons and to eliminate any effects on the evaluation of study drugs.
12. Set in addition to the above to ensure that subjects inappropriate for participation from scientific and ethical points of view would be excluded from this study.

6. Research plan

6.1. Study design

A multicenter, randomized, placebo-controlled, double-blind trial.

6.2. Target sample size

100 patients

AJG533 (elobixibat) placebo-treated group: 50 patients
AJG533 (elobixibat) 10 mg group: 50 patients

6.3. Study period

Enrollment time: From the date of jRCT publication (MHLW Notification) to July 31, 2022
Study period: From the date of jRCT publication (MHLW notification) to November 30, 2023
(approximately three years)

Expected duration of participation of subjects: Up to 17 weeks after obtaining informed consent
Observation period: two to four weeks
Treatment period: 12 weeks (up to 13 weeks)

6.4. Institutional registration, case registration, and allocation methods

Facilities will be registered via a central registration system at the data center. Case enrollment will be possible from medical institutions that have completed the facility registration process.

6.4.1. Data center

Clinical Trial Data Management Office, Yokohama City University Hospital Next Generation Clinical Research Center (Y-NEXT)

TEL: 045-370-7976; FAX: 045-370-7954
Mail: ynextdc@yokohama-cu.ac.jp

Hours: Weekdays 9:00–17:00 (excluding Saturdays, public holidays, and the beginning of the year (December 29th–January 3rd))

6.4.2. Facility registration

The supervising physician at each implementing medical institution will obtain approval regarding the study implementation from administrators at each implementing medical institution after approval by the accredited clinical research review committee. After that, administrators’ implementation approval forms (copies) from each implementing medical institution will be sent to
the data center. The data center will register the facility and notify the investigator by sending a notification of completion of facility registration.

6.4.3. Enrollment and allocation of subjects

The principal investigator or a sub-investigator shall grant a Subject Identification Code for all subjects who have obtained informed consent. Eligibility tests will be performed, and registration-related information will be entered into the eCRF registration form at enrollment, and stored. The case registration number will be displayed on the EDC system screen for cases judged to be eligible. The case registration number will be recorded on the subject screening list. The supervising physician or the sub-investigator will enter the allocation-related information of subjects who met the treatment initiation criteria after the run-in period into eCRF: allocation form at the time of allocation; this information will be stored. The study drug with the labeled drug number will be prescribed, and the drug number will be recorded in the subject screening list.

Re-enrollment will be allowed for subjects who do not meet the treatment initiation criteria and those who have dropped out before treatment. In such cases, informed consent will be obtained again from the subject, and eligibility tests etc. will be reperformed and confirmed.

6.4.4. Allocation methods and allocation adjustment factors

After confirming that the subjects meet the treatment initiation criteria, they will be assigned to treatment groups according to the study drug allocation code table created using the replacement block method. No other methods have been established.

6.4.5. Means of blinding

Blinding will be accomplished using a comparator (placebo tablet) that is indistinguishable from the study drug.

6.4.6. Determination of the necessity of and procedure for unblinding of the emergency key codes

1. When a supervising physician or a sub-investigator judges that it is necessary to know the key code of the investigational product in use (e.g., in cases of serious illness, adverse events, etc.), he/she contacts the principal investigator and asks the physician to take action for breaking the emergency key code.

2. When it is judged that an emergency key code will be unblinded, the principal investigator asks the storage manager of the emergency key code to perform the unblinding.
3. When the emergency key code is unlocked by the person responsible for storing the emergency key code, the key code of the case shall be immediately notified by the principal investigator to the supervising physician or sub-investigator.

4. The principal investigator shall keep a record of the subjects informed of the key code as well as the reason for determining that unblinding of the emergency key code was necessary.

6.4.7. Unblinding of study drug allocation code tables

The study drug allocation manager unlocks the research drug allocation code table after all eCRFs are created and the data are fixed.

6.5. Treatment planning

6.5.1. Protocol for treatment

6.5.1.1. Observation period

Observation period: 2-4 weeks

Subjects will maintain a patient diary daily during the observation period.

6.5.1.2. Protocol treatment phase
After completion of the run-in period, the treatment initiation criteria will be confirmed, and the administration of the study drug will begin on the day of allocation. A patient diary will be maintained daily for the duration of the treatment.

AJG533 placebo group: AJG533 placebo (2 tablets) orally once daily prior to meals for 12 weeks.
AJG533 10 mg group: AJG533 10 mg (5 mg×2 tablets) orally once daily prior to meals for 12 weeks.

6.5.2. Concomitant medication/treatment

6.5.2.1. Restricted concomitant medications: Time from the run-in period to the end of the treatment period (last dose)

Drugs that can be used in a limited manner are listed below. The frequency of use and other parameters will be investigated and recorded.

The rescue medication prescribed for this study (bisacodyl suppository 10 mg/1 tablet once and Pursennid tablet 12 mg/2 tablets once) may be used in the following conditions:

- Bisacodyl suppository 10 mg/1 tablet once or Pursennid tablets 12 mg/two tablets once can be used as rescue medication only if bowel movements are not observed for two or more consecutive days.
- The investigator or sub-investigator will decide whether the patient should continue the study if bowel movements are not observed after using one bisacodyl suppository 10 mg/dose or two Pursennid tablets 12 mg/per dose.
- If after the use of the rescue medication, bowel movements are observed but are subsequently not observed for at least two consecutive days, rescue medication (10 mg/1 tablet bisacodyl suppository and 12 mg/2 Pursennid tablets) may be used once more.

6.5.2.2. Prohibited concomitant drugs/therapies/procedures: From the start of the run-in period to the end of the treatment period (last dose)

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The following drugs, therapies, and procedures that may affect this study are prohibited:

- Various laxatives (magnesium oxide preparations, sodium picosulfate, sennoside, etc.) *excluding rescue drugs
- Bile acid transporter inhibitors other than the study drugs
- Chinese herbal medicines with indications for constipation (Daio-kanzoto, Dai-kanzo-to, Dai-ko-to, Dai-saiko-to, etc.)
- Sensitive enterosynchronous pharmaceuticals (hydrochloric acid Ramosetron, polycarbophil calcium, trimebutine maleate, etc.)
- 5-HT3 antiemetics
- Gastrointestinal prokinetics (mosapride citrate, metoclopramide, domperidone, etc.)
- Macrolide antibiotics (erythromycin, roxithromycin, azithromycin, etc.)
- Antidepressants, antipsychotics, anxiolytics, and tranquilizers (excluding those used for insomnia treatment)
- Anticholinergic drugs (excluding topical)
- Over-the-counter drugs and supplements for the improvement of constipation, etc.
- Enema and irrigation
- Intestinal cleansers
- Bile acid preparations (ursodeoxycholic acid, chenodeoxycholic dehydrocholic acid)
- Aluminum-containing antacids (sucralfate hydrate, aldioxa, etc.)
- Cholestyramine and cholestidime
- Biofeedback and other treatments for constipation
- Stool removal
- Lower gastrointestinal endoscopy

6.5.2.3 Precautions for concomitant use during treatment (until the last dose)

Drugs requiring caution on concomitant use are as follows:

- Digoxin, dabigatran etexilate methanesulfonate
- Mitazolam

6.5.3. Guidance for subjects

Supervising physicians and sub-investigators will hand over the patient diary to the test subject, explain the procedures for completing the diary and taking the drug, and instruct the subject to pay attention to the following points:

1. Patients must not radically change their lifestyle with reference to diet and exercise during the study period.
2. Patient diaries will be provided to patients at the time of enrollment. The patients must record the status of their bowel movements, drug compliance, and any use of rescue medications every day.

3. Patients will be instructed to make entries from the start date of the run-in period to the end date of the oral administration of the study drug in their patient diaries.

4. When visiting other hospitals, patients must inform physicians of their participation in this study. Patients must inform supervising physicians or sub-investigators in advance if they plan to visit another hospital or receive a new prescription drug or treatment or are subjected to examination.

5. Patients must make every effort to visit their clinics on the prescribed days. If they are unable to do so, they must inform the clinic in advance.

6. Patients must inform the investigator or sub-investigator about the drugs, supplements, and treatments concomitantly taken, including prescription drugs at other hospitals and over-the-counter drugs purchased at pharmacies.

7. Patients must take the study drug (two tablets) once a day before meals from the day of allocation according to the instructions of the supervising physician or sub-investigator.

8. If a patient misses a dose, they must try to take the drug as soon as possible on the same day.

9. Patients should always bring any remaining drugs and empty sheets (resulting from missed doses) as well as their patient diary with them to their next visit.

10. Patients should mandatorily bring stools collected at the time of presentation (V2, V3, and V5).

11. Patients who are women of childbearing potential must use appropriate contraceptives from the time of obtaining informed consent to the end of the treatment period.

6.5.4. Criteria for dose reduction and withdrawal
Not applicable.

6.5.5. Criteria for dose increase and resumption
Not applicable.
7. Observation, examination, investigation, and evaluation items

7.1. Schedule table

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Observational period</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V1</td>
<td>V2/Randomisation</td>
</tr>
<tr>
<td></td>
<td>Registration</td>
<td>Randomisation</td>
</tr>
<tr>
<td>Visit Window</td>
<td>-</td>
<td>2–4 weeks after registration</td>
</tr>
</tbody>
</table>

| Informed consent | ○                  | ○                | ○    | ○    | ○    |
| Inclusion/exclusion criteria | ○                | ○                | ○    | ○    | ○    |
| Demographics     | ○                  | ○                | ○    | ○    | ○    |
| Vital signs/height and weight | ○           | ○                | ○    | ○    | ○    |
| Blood test       | ○                  | ○                | ○    | ○    | ○    |
| Registration     | ○                  | ○                | ○    | ○    | ○    |
| Confirmation of administration start criteria/allocation | ○                | ○                | ○    | ○    | ○    |
| Blood and stool collection for exploratory research | ● | ● | ● | ● |
| Providing drugs  | ○                  | ○                | ○    | ○    | ○    |
| Checking the medication status | ○        | ○                | ○    | ○    | ○    |
| Review concomitant medications | ○           | ○                | ○    | ○    | ○    |
| Review rescue drugs | ○        | ○                | ○    | ○    | ○    |
| Review adverse events |                | ○                | ○    | ○    | ○    |
| Questionnaire/Review patient diary | ○       | ○                | ○    | ○    | ○    |
| Patient diary confirmation |                | ○                | ○    | ○    | ○    |

Θ After confirming the treatment initiation criteria, drugs will be allocated.
● Test stool collection kits should be provided mandatorily in the previous visit.

a: The patient's vital signs include blood pressure and pulse rate will be recorded. Height and weight will be measured only at enrollment.
b: Patient diaries will be provided on V1, and diary entries will be checked at each visit.

7.2. Implementation schedule and evaluation items

7.2.1. Prior to obtaining or registering consent

1) Inclusion and exclusion criteria
2) Subject characteristics
   Sex, age (at the time of informed consent)
Date of consent

History: Diseases that may affect the efficacy and safety of the target drug (within the past one year), presence or absence of previous laparotomy

Complications: major underlying diseases, etc. at the time of informed consent

3) Subjective/objective symptoms
4) Vital signs: blood pressure, pulse rate
5) Height and weight
6) Hematologic: white blood cell count, hemoglobin, and platelet count
7) Biochemical tests: total protein, albumin, AST, ALT, γ-GTP, ALP, total bilirubin, urea nitrogen, creatinine, uric acid, LDL-cholesterol, HDL-cholesterol, total cholesterol, Na, K, Cl
8) Review of concomitant medications
9) Explanation and provision of patient diaries

7.2.3. Before allocation

1) Confirmation of treatment initiation criteria
2) Vital signs: blood pressure, pulse rate
3) Subjective/objective symptoms
4) Blood and stool collection for exploratory research
5) Review of concomitant medications
6) Survey of rescue drugs
7) Investigations of adverse reactions
8) Questionnaire-based survey (JPAC-QOL)
9) Review of patient diaries (time of day, frequency of bowel movements, BS score, presence of feeling of residual stool, degree of straining, and presence or absence of intention to defecate)

7.2.4. Treatment period: 4, 8 weeks

1) Vital signs: blood pressure, pulse rate
2) Subjective/objective symptoms
3) Checking compliance
4) Performed only at 4 of week of blood/stool collection for exploratory studies
5) Review of concomitant medications
6) Survey of rescue drugs
7) Investigations of adverse reactions
8) Questionnaire-based survey (JPAC-QOL) conducted only at 4 weeks
9) Reviewing the patient diary (date and time, frequency of bowel movements, BS score, presence of feeling of residual stool, degree of straining, and presence or absence of intention to defecate)

7.2.5. Treatment period 12 weeks/EOT
1) Vital signs: blood pressure, pulse rate
2) Subjective/objective symptoms
3) Hematology: white blood cell count, hemoglobin, and platelet counts
4) Biochemical tests: total protein, albumin, AST, ALT, γ-GTP, ALP, total bilirubin, urea nitrogen, creatinine, uric acid, LDL-cholesterol, HDL-cholesterol, total cholesterol, Na, K, Cl
5) Compliance check
6) Blood and stool collection for exploratory research
7) Review of concomitant medications
8) Survey of rescue drugs
9) Investigations of adverse reactions
10) Questionnaire-based survey (JPAC-QOL)
11) Checking the patient diary (date and time, frequency of bowel movements, BS score, presence of feeling of residual stool, degree of straining, and presence or absence of intention to defecate)

7.3 Evaluation method
Not applicable to this study.

8. Consent
8.1. Informed consent
Prior to participating in the study, the supervising physician and sub-investigators will answer the subject's questions using the consent and explanatory documents approved by the certified clinical research review board as described in the implementation plan. Enough time will be given to the subjects to decide on whether to participate in the study. After confirming that the subject has fully understood the content, informed consent for participation will be obtained in writing. When new information, unknown and unexpected at the time of consent, is obtained that might affect the subject's willingness to participate, the informed consent/explanatory document will be promptly revised. This revision will be explained using the consent/explanatory document approved by the certified clinical research review board, and the subject's willingness to participate in the
study will be confirmed again prior to obtaining informed consent. In addition, re-consent will be obtained in the same manner when changes are made to the study content, etc. The subject will be informed that even after agreeing to participate in the study, it is possible to withdraw consent at any time if they wish. When withdrawing consent, the principal investigator and sub-investigator shall consult with the subject whenever possible to ascertain the reason for withdrawing consent, and explain about how to treat constipation after withdrawing consent. Then, the subject's withdrawal of informed consent will be obtained by the withdrawal of informed consent.

8.2. Response to consultations by subjects and their associated persons

The supervising physician or sub-investigator will respond to queries received from the study subjects etc. and related persons. If unsure on how to respond, they will respond after discussing with the research office in accordance with the content of the queries.

8.3. When informed consent is obtained from the representative, etc.

Not applicable to this study because all subjects will be aged 20 years or older and will be able to provide written informed consent for participation in this study.

8.4. When obtaining informed assent

Not applicable to this study.

8.5. When obtaining informed consent for test subjects is not necessary

Not applicable to this study.

9. Evaluation items

9.1. Primary endpoint

Change in the number of CSBMs at Week 12 of the treatment period than at Week 2 of the run-in period

* SBMs without a feeling of residual stool

[Definition]

One week before the end of study drug administration is defined as Week 12 of the treatment period. One week prior to the start of study drug administration is defined as Week 2 of the run-in period. The number of CSBMs per week (seven days) is the total number of CSBMs per week. However, if CSBMs occur less frequently than four days/week, this will be treated as missing data.

[Rationale]
Prior literature has set the primary endpoint as 'spontaneous bowel movements' [2], whereas this study included 'complete spontaneous bowel movements', which represents the frequency of bowel movements assessed for QOL; this has been set in the EMA guidelines in the recent years [15]. Previous studies have shown significant differences at Week 2, but chronic constipation is defined as unsatisfactory bowel movements for three months or longer. Efficacy after two weeks of administration does not necessarily indicate an improvement in the chronicity of constipation. To demonstrate this efficacy, the change in CSBMs after 12 weeks of administration was set as our primary endpoint [16].

9.2. Secondary endpoints

- Change in the number of CSBMs for each week between Weeks 1 and 11 of the treatment period relative to Week 2 of the run-in period
- Change in the number of SBMs for each week of the treatment period relative to Week 2 of the run-in period
- Percentage of responders ** as per the number of SBMs and the number of CSBMs for each week of the treatment phase

** Individuals for whom the frequency of SBMs and CSBMs per week increased by at least one relative to Week 2 of the run-in period, and for whom the frequency of bowel movements is more than three times a week.

- Percentage of responders⁶ as per the number of CSBMs during the treatment period (12 weeks)

Defining ⁶ Responders: Those showing recovery of at least one or more CSBMs weekly and at least three CSBMs relative to baseline during 9 of 12 weeks of treatment, including at least Weeks 9-12 of the treatment period

- Percentage change in stool consistency based on the Bristol Stool Properties Scale at each week of the treatment period, relative to Week 2 of the run-in period
- Percentage change in the presence or absence of residual stool at each week of the treatment period, relative to Week 2 of the run-in period
- Percentage change in the degree of straining at each week of the treatment period, relative to Week 2 of the run-in period
- Percentage change in the presence or absence of bowel movements at each week of the treatment period, relative to Week 2 of the run-in period
- Change in JPAC-QOL scores at Week 4 and Week 12, relative to baseline (V2)
- Changes in the following at Week 4 and Week 1, relative to baseline (V2):
  1. Changes in the absolute values and percentages of fecal gut microbiota.
2. Changes in the absolute values and percentages of blood and fecal bile acids
3. Changes in the absolute values and percentages of fecal organic acids
4. Changes in the absolute values and percentages of blood and fecal amino acids
5. Changes in blood C4

9.3. Safety endpoint
   * Incidence of adverse events

10. Discovery research
    In this study, blood and stool samples will be collected.
    The purpose of this study is to investigate the effects of increasing bile acids by study drugs, on
    the intestinal microbiota, etc.
    Bile acid fraction, amino acid fraction, and C4 will be measured in the blood, and intestinal
    microbiota, bile acid fraction, organic acid fraction, and amino acid fraction will be measured in the
    feces; exploratory analysis will be performed.

10.1. Timing of sample collection and transport
    Each sample will be collected at the times indicated in "7.1. Schedule tables". Each sample will
    be processed according to the procedure manual prepared separately, and will be transported to the
    Department of Hepatobiliary and Pancreatic Gastroenterology, Yokohama City University. After
    transport, stools will be stored at below 0 °C, and blood will be stored appropriately in a freezer at
    below -20 ºC.
    A portion of the stool sample will be sent to the Pharmacology Department, Shimane University
    School of Medicine; this is an institute that performs analyses of gut microbiota. Samples will be
    delivered with the case registration number (anonymized) as per the procedure manual. Only the
    samples will be sent, and the corresponding tables etc. will not be provided. After the analysis, the
    institute will discard the samples. The results of the analysis will be provided to the data center via
    a password-protected electronic document.

10.2. Control, storage, and disposal of samples
    Each sample will be stored with the case registration number allocated after registration in this
    study.
    After measurement, samples will be stored using the Sample Control Table at the Department of
    Hepatobiliary and Pancreatic Gastroenterology, Yokohama City University
    The remaining specimens will be kept in storage for a period of five years starting from the day of
    the final analysis.
Nail samples will be discarded unless otherwise specified.

When consent is withdrawn, the anonymization number etc. will be removed and discarded appropriately.

10.3. Withdrawal of consent for the use of the sample

When a subject withdraws consent for the use of their donated sample, the sample will be disposed of/discarded and will not be used in the study. However, if the study results have already been published at the time of withdrawal of consent, the results will not be discarded.

Additionally, if measurement/analysis has already been performed, it is not mandatory to discard the results.

Supervising physicians will confirm that the following are performed:

1. The withdrawal of the subject's consent for the use of the donated sample has been reported immediately. If the specimens collected from the subject are stored at the medical institution, they should be immediately identified, disposed/discarded, and documented.
2. The agency storing and analyzing the sample has been immediately informed of the withdrawal of consent; the sample was disposed/discarded, and this was recorded.
3. The disposal/discarding of the sample has been reported to the subjects and principal investigator.

11. Storage and Storage of Samples and Information

11.1. Storage and disposal of samples

In this study, blood and stool samples will be collected as part of an exploratory study. The procedures for storage, disposal etc will be followed as described in "10. Exploratory studies".

11.2. Storage and storage period for information

The supervising physician will strictly store information on paper other than the medical records listed below in a lockable archive. Information on electronic media will be stored in an electronic recording medium, such as a personal computer or a USB memory drive, independent of LAN or the Internet with a password and will be stored strictly in a lockable repository when not in use. When the computer used in this study is connected to the Internet or to hospital-based LANs, appropriate security measures will be employed, such as installing anti-virus software; the connection will be managed in compliance with the security policies, etc. at each facility, such as not connecting where a large number of unspecified lines or public LANs can be connected. The storage period will be five years from the end of the study. After the set storage period, the documents and records will be disposed of with utmost care to ensure that personal and confidential information is not leaked. Papers will be shredded using a shredder and discarded. Other media with
details given below will be discarded by appropriate methods such as deletion after anonymization has been performed.

- Items that identify subjects (corresponding table)
- Items related to medical care and examination of test subjects
- Protocol, study brochure, source documents, etc.
- Subject information and informed consent form
- Agreement (signed original)
- Primary endpoint reports, clinical study reports, and overview
- Notification of review results received from the accredited clinical research review board, etc.
- Copies of reports other than the implementation plan sent to the MHLW
- Monitoring documentation
- Contract for the conduct of specific clinical research
- Records related to the management of drugs, etc.
- Other important research documents designated by research representatives

11.3. Secondary use of samples and information

The information and research data obtained from this study may be used for different purposes or may be provided to other research institutions by the researchers involved in this study; this will be carried out after the development of a new study protocol and approval by the Ethics Review Board. Informed consent will be obtained in an appropriate manner according to the content of the study.

11.4. Use of samples and information as biobanks

Not applicable.

12. Handling of diseases

12.1. Definition of diseases, etc.

Adverse events suspected to be attributable to this study, including diseases, disabilities, deaths, infections, and various other symptoms, will be classified as "diseases, etc." The results of clinical studies will be analyzed in relation to the drug used in the study or to the study procedure. Causality will be determined by the investigator, sub-investigator, or principal investigator based on “Section 12.3, Causal relationships with the study.”
12.2. Evaluation of diseases

In this study, the degree of illness, etc. occurring between the time of enrollment and the end of oral administration of the study drug will be evaluated as follows:

1) Mild: Conditions in which drug administration can be continued without treatment
2) Moderate: Conditions in which drug administration can be continued with any treatment
3) Severe: Conditions in which drug administration is or should be discontinued.

12.3. Causal relationships with the study.

Causality will be assessed according to the following criteria:

**Causal relationship is undeniable:** The decision should be made according to the following, regardless of whether it is known that the event in question was caused by the study or interventional treatment:
- The event is reasonably or possibly reasonably attributable to the study or interventional treatment.
- There is a temporal relationship between the event and the study.
- No other cause is apparent, and a causal relationship to the study cannot be ruled out.

**Not related:** Judged according to the following criteria:
- Not reasonably attributable to the study or interventional treatment
- Shows no temporal relationship
- Other causes indicated

12.4. Predictability

Predictability determinations will be conducted in accordance with the package insert and interview forms, etc., as the study drug is to be used within the approved indication.

12.4.1 Predicted possible diseases, etc.

Elobixibat: In domestic clinical studies up to the time of approval, adverse drug reactions including abnormal laboratory test values were observed in 292 (46.3%) of 631 patients. The main side effects were abdominal pain in 120 cases (19.0%) and diarrhea in 99 cases (15.7%). Other side effects are as follows.
<table>
<thead>
<tr>
<th></th>
<th>&gt;5%</th>
<th>&lt;1-5%</th>
<th>&lt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Liver function test abnormal (ALT (GPT) increase, AST (GOT) increase).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychoneurological</td>
<td></td>
<td>Headache, dizziness</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td>Hot flushes</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Abdominal pain (19.0%), diarrhea (15.7%), lower abdominal pain, and abdominal distention</td>
<td>Nausea, upper abdominal pain, Abdominal discomfort, loose stools</td>
<td>Flatulence, dry mouth, fecal urgency, Vomiting, abnormal gastrointestinal sounds, constipation, stomatitis</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
<td></td>
<td>Urticaria, rash</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td>Elevated eosinophil counts, anemia, Elevated vitamin E levels</td>
</tr>
<tr>
<td>Other</td>
<td>Increased CK (CPK)</td>
<td></td>
<td>Dysmenorrhea</td>
</tr>
</tbody>
</table>

12.5. Measures to be taken in the event of a disease, etc.

12.5.1. Measures for subjects

In the event of a disease, etc., to ensure the safety of the subject, the supervising physicians and sub-investigators will take appropriate measures such as treatment and discontinuation of research drug administration as necessary. If treatment is required, the subject will be informed to that effect.

If the adverse event continues at the time of the final observation at the end of the study, the investigator or sub-investigator will follow up until the condition recovers to the baseline state or stabilizes clinically.

12.5.2. Evaluation and documentation

Supervising physicians or sub-investigators will record the following in the original documents (medical records, etc.) if a disease, etc., occurs: the name of the disease, date of onset, severity, seriousness, non-seriousness, reason that it is judged to be serious, details of treatment/therapy, causal link to the study and study drug, date of outcome, outcome (recovery, remission, not recovered, with sequelae, death, unknown), reason for termination of the outcome (not recovered, death, unknown), etc.

12.5.3. Reporting of serious diseases, etc.
In the event that a disease, etc. occurs as per the following 1-7 points, the study sub-investigator who becomes aware of this shall report the relevant information to the supervising physician of their institution. Supervising physicians receiving such reports will then report them to the administrator at their medical institution and inform the principal investigator. Subsequently, according to the predictability of the disease, this information will be reported to the certified clinical research review board between the time the principal investigator becomes aware of it and the following reporting time limit.

1. May or did lead to death
2. May require admission to a medical institution or prolonged hospital stay for treatment
3. May or did lead to disability
4. Serious according to points 1-3
5. Congenital disease or abnormality in later generations
6. Points 1-5 as a result of infection
7. Diseases etc. caused by infections, etc. that do not correspond to point 6 (non-serious illnesses caused by infectious diseases, etc.)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Diseases, etc.</th>
<th>Predictability, etc.</th>
<th>Due date for reporting to managers and committees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-infectious diseases</td>
<td>1. Death</td>
<td>Not applicable</td>
<td>15 days</td>
</tr>
<tr>
<td></td>
<td>2. Diseases etc. requiring admission to a medical institution or prolonged hospital stay for treatment</td>
<td>Other, cannot be predicted</td>
<td>15 days</td>
</tr>
<tr>
<td></td>
<td>3. Disorders</td>
<td>Other, cannot be predicted</td>
<td>15 days</td>
</tr>
<tr>
<td></td>
<td>4. Diseases that may lead to death or disability</td>
<td>Other, cannot be predicted</td>
<td>15 days</td>
</tr>
<tr>
<td></td>
<td>5. Serious illnesses in accordance with the diseases etc. listed in 2. to 4. above</td>
<td>Other, cannot be predicted</td>
<td>15 days</td>
</tr>
<tr>
<td></td>
<td>6. Any congenital disease or anomaly in the offspring of a treated patient.</td>
<td>Other, cannot be predicted</td>
<td>15 days</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>7. Diseases etc. caused by infections</td>
<td>Unpredictable</td>
<td>15 days</td>
</tr>
<tr>
<td></td>
<td>8. Diseases etc. listed above in 1. to 7. caused by infections (excluding 7.)</td>
<td>Not applicable</td>
<td>15 days</td>
</tr>
</tbody>
</table>
1) Occurrence of infectious diseases associated with hematologic toxicity shall be classified as "non-infectious diseases."

2) Either predictable or unpredictable based on the information given in the package inserts or interview forms for the drugs, etc. used in the specified clinical study. Trends of occurrence cannot be predicted or changes in the trends of occurrence may result in the occurrence or spread of health hazards.

3) Those that cannot be predicted from the "Precautions" section of the drug package insert.

12.5.4. Reporting of other diseases, etc.

Occurrence of diseases, etc. suspected to be attributable to the conduct of the specified clinical research (all of those mentioned above).

Reports (excluding periodic reports) (within two months after the expiration of the period) will be submitted to the Minister of Health, Labor, and Welfare annually from the date of submission of the implementation plan.

When a disease, etc., is known to have occurred, the supervising physician at each participating medical organization will inform the supervisor of the participating medical organization when making periodic annual reports, and then inform the principal investigator. The principal investigator will report the disease to the accredited clinical research review board described in the implementation plan. In addition, the principal investigator will promptly provide information to other supervising physicians, and the other supervising physicians will promptly report the content of such information to the administrators of the participating medical organizations.

12.5.5. Response to the opinions of the accredited clinical research review board

When opinions are provided by the committee, the principal investigator conducts opinions from the committee.

Reports will be made to administrators of medical institutions. Specific based on the opinions of the committee

Reports to the administrators of the participating medical organizations will be sent, including the content of the response, if necessary.

The principal investigator will provide information to the supervising physicians, and the supervising physicians will promptly report this information to the administrators of the participating medical organizations.

12.5.6. Reporting of deficiencies

Not applicable.
12.6. Adverse events excluding diseases, etc.

12.6.1. Definition of adverse events

An adverse event is any unfavorable or unintended injury or disease (including an abnormal laboratory test result) occurring in a subject, whether or not it is causally related to the study drug. This includes exacerbations of existing disease (not pathogenic) during the study period. However, if an illness or other condition is relevant, it shall follow from 12.1 to 12.3.

12.6.2. To evaluate adverse events

For the evaluation of adverse events, proceed as directed in sections 12.2 to 12.4.

12.6.3. Measures for subjects

The procedure given in section 12.5.1 shall apply to subjects.

12.6.4. Evaluation and documentation

Section 12.5.2 shall apply mutatis mutandis to the evaluation and recording of the relevant information.

12.6.5. Serious adverse event report

In the event of the occurrence of a serious adverse event, excluding diseases, etc., at any participating medical institution in this multicenter clinical study, the supervising physician at the participating medical organization will promptly report the occurrence to the principal investigator. The principal investigator will inform the supervising physicians at each participating medical institution, as needed. The investigator shall not be required to report serious adverse events excluding diseases, etc., to the administrators of the participating medical organizations.

13. Discontinuation criteria and procedures

13.1 Discontinuation criteria

Subjects will be withdrawn from the study if they meet any of the following criteria:

1. When they request to withdraw consent
2. When it is found after registration that the subject does not meet the inclusion criteria or meets the exclusion criteria, and it is deemed that participation by the subject is inappropriate
3. When it is determined that the patient does not meet the criteria for the starting dosage after allocation
4. When it is difficult to continue the study due to worsening symptoms and disease findings
5. When it is difficult to continue the study due to the occurrence of an adverse event
6. When there is significant deviation from the protocol
7. Death
8. When pregnancy occurs
9. Other than the above, when the supervising physician or the sub-investigator judges that it is not favorable for the subject to continue to participate the study

13.2 Discontinuation procedure
When a test subject meets the criteria for withdrawal, the supervising physician or the sub-investigator will explain this to the relevant test subject, discontinue the study, and take appropriate measures. In addition, if it is determined that the patient is ineligible at enrollment, CRF preparation will not be required, and the study will be terminated without handling discontinuation. When a subject requests to withdraw from the study, appropriate efforts will be made to fully respect the rights of the subject and to ascertain the reason for requesting withdrawal.

1. Discontinuation procedure prior to taking the study drug
   If the subjects discontinues study participation without taking the study drug, the supervising physician or the sub-investigator will record the date of discontinuation (date on which discontinuation was judged) and the reason for discontinuation in the Case Report Form. If the study drug was provided, the unused study drug will be collected at the subject's visit.

2. Discontinuation procedure after taking the study drug
   Unless the cooperation of the test subject cannot be obtained, the status of study drug administration (during the treatment period) and the occurrence of adverse events will be investigated, and tests and evaluations specified at the time of discontinuation will be performed. The supervising physician or the sub-investigator will record the date of discontinuation (date on which discontinuation was judged) and the reason for discontinuation in the Case Report Form. If discontinuation occurs during the treatment period, the remaining drugs and empty packs that have been opened, etc., will be collected at the subject's visit. As a rule, supervising physicians or sub-investigators will conduct a follow-up study when adverse events are observed.

13.3 Post-treatment after completion (discontinuation) of protocol treatment
   Not applicable.
14. Discontinuation of the study

The entire study may be discontinued if the following situations occur and the principal investigator, certified clinical research review board, or supervisor of the participating medical institution decide that it should be discontinued.

- When unexpected serious disease, etc. occurs, and there is concern that significant harm may befall all subjects.
- If the intervention is deemed to be ineffective
- Sites where significant breaches/non-compliance with regulations and related procedures or study protocols have been identified
- When facts that may compromise ethical or scientific rationality are obtained
- When a significant risk to subjects is identified
- If recommended to do so by the Accredited Clinical Research Review Board
- In the event the Minister of Health, Labor and Welfare receives a request or recommendation for discontinuation of the study

In the event of discontinuation, the principal investigator will report to the supervising physicians at all participating medical organizations, the certified clinical research review board, and the administrators of the participating medical organizations. In addition, subjects will be contacted and informed about changes in the study schedule. In addition, subjects will be promptly informed of this, and coordination of the next visit will be performed to confirm safety.

The principal investigator will also prepare a Unified Form 11 discontinuation notification within 10 days of the discontinuation date and inform the certified clinical research review board. The principal investigator will prepare the Form 4-specified clinical research termination notification and will notify the Ministry of Health, Labor, and Welfare. Even if the study is discontinued, the primary endpoint reports, clinical study reports, and summaries will be prepared appropriately, and periodic reports and disease reports will be made until the study is completed.

15. Efficacy and safety evaluation committee

An efficacy and safety evaluation committee has not been established for this study.

16. Statistical analysis

Details will be specified separately in the statistical analysis plan (prepared finalizing the data).

16.1. Analysis sets

The following three analysis populations are defined:

16.1.1. Full analysis set (FAS)
This population will consist of those remaining after the following have been excluded from the set of all enrolled subjects:

- Subjects who violate critical inclusion/exclusion criteria
- Subjects who never received the protocol treatment
- Subjects for whom no data other than the information obtained at the time of enrollment in the study has been collected after enrollment

16.1.2. Per-protocol set (PPS).

This population consists of the FAS after subjects who fall under the following have been excluded:

1) Subjects who received a drug different from the study drug in the assigned treatment group
2) Subjects with missing primary endpoint data
3) Subjects with problems, such as those who engaged in the use of prohibited concomitant medications, exhibited poor compliance, could not be followed-up, or have missing data”

“Detailed criteria for sampling shall be separately set forth in the Criteria for case sampling.

16.1.3. Safety analysis set (SAS)

This population consists of all subjects who have received at least one dose of the study drug.

16.2. Rationale for setting the target number of patients

The target enrollment number will be 50 patients per group, totaling 100 patients.

In a previous Phase II study [17] in Japan, the secondary endpoint was the change in CSBM in Weeks 1 and 2 relative to Week 2 of the run-in period; in that study, 38 to 40 patients in the elobixibat 10 mg group showed a significant improvement versus placebo (p=0.0032, p=0.0004, respectively).

Previous Phase 3 study [18] showed that CSBM change relative to Week 2 of the run-in phase to Week 2 was 2.98 ± 3.1 (mean ± SD) in the elobixibat group (n=65) and 0.86 ± 1.45 in the placebo-treated group (n=63).

Additionally, in another previous study, the change in CSBM at Week 2 of the treatment period relative to Week 2 of the run-in period was calculated to be 2.12 for the between-group difference, and approximately 2.288 for the common-standard deviation. Since the study period for this study is longer than that for the previous study, it is assumed that the difference between the mean values of the groups will be small, while the variation in the difference between groups in the amount of change will be larger due to the differences with reference to participating medical institutions in the previous study.

Therefore, in designing the sample size for this study, it was assumed that the between-group differences and common-standard-deviations for the primary endpoint (CSBM change relative to
Week 2 of the run-in period at Week 12 of the treatment period) will be 1.8 and 2.5, respectively. At this time, a Student's t-test provides a two-sided significance level of 5% and a power of 90% for 42 patients per group.

Since the study period is longer than that of the previous study, a dropout rate of approximately 10% was assumed, and a total of 100 patients (50 per group) was selected to ensure adequate power.

16.3. Statistical analysis
The significance level used for testing and estimation will be 5% (two-sided) unless otherwise stated.

16.3.1. Primary endpoint analysis
16.3.1.1. Primary analysis
The main analysis will be for FAS, and the change in the number of CSBMs at Week 12 of the treatment period relative to Week 2 of the run-in period will be analyzed for covariates, including the number of SBMs at Week 2 of the run-in period.

16.3.1.2. Secondary analysis
The secondary analysis will be similar to the primary analysis in PPS. To supplement the results of the primary analysis, the missing status of the primary endpoint will be summarized as needed.

Adjusted analyses will be conducted with subject background factors as covariates.

Subgroup analyses will be conducted with subject background factors categorized into appropriate categories.

16.3.2. Analysis of the secondary variables
1) Change in the number of CSBMs per week between Weeks 1 and 11 of the treatment period relative to Week 2 of the run-in period.
For FAS, the change in the number of CSBMs in the treatment groups at Weeks 1 to 11 of the treatment period relative to Week 2 of the run-in period will be compared and analyzed for covariance with the number of CSBMs at Week 2 of the run-in period as a covariate.

2) Change in the number of SBMs relative to Week 2 of the run-in period for each week of the treatment period.
For the FAS, the change in the number of SBMs in the treatment groups at each week of the treatment period relative to Week 2 of the run-in period will be compared and analyzed for covariance, with the number of SBMs at Week 2 of the run-in period as a covariate.

3) Percentage of responders with reference to the number of SBMs and the number of CSBMs for each week of the treatment phase.
FAS will be included and the percentage of responders with reference to SBMs and CSBM will be compared between treatment groups at each week of the treatment phase using the Fisher's exact test.

4) Percentage of responders with reference to the number of CSBM during treatment (12 weeks). The percentage of responders with reference to CSBM in the FAS for the duration of the treatment (12 weeks) will be compared using the Fisher's exact test.

5) Percentage change in stool consistency based on the Bristol Stool Properties Scale at each week of the treatment period relative to Week 2 of the run-in period.
   For the FAS, stool consistency will be compared between treatment groups at each week of the treatment phase using the Wilcoxon rank sum test.

6) Percentage change in the presence or absence of residual stool at each week of the treatment period relative to Week 2 of the run-in period.
   For the FAS, the presence or absence of the feeling of residual stool will be compared between the treatment groups at each week of the treatment period using the Fisher's exact test.

7) Percentage change in the degree of straining at each week of the treatment period relative to Week 2 of the run-in period.
   In the FAS, the degree of straining will be compared between the treatment groups at each week of the treatment period using the Wilcoxon rank sum test.

8) Percentage change in the presence or absence of bowel movements at each week of the treatment period relative to Week 2 of the run-in period.
   In the FAS, the urge to defecate will be compared between the treatment groups at each week of the treatment period using the Fisher's exact test.

9) Change in JPAC-QOL scores at Week 4 and Week 12 relative to baseline (V2).
   In the FAS, changes in JPAC-QOL scores at each time point during the treatment period relative to baseline (V2) will be analyzed for covariates.

10) Changes in absolute values and percentages in gut microbiota at Week 4 and Week 12 during the treatment period relative to baseline (V2).
    In the FAS, the absolute abundance and change in percentages of gut microbiota with percentages ≥0.1% will be compared between treatment groups. FDR-correction using the Benjamini-Hochberg method applied, and the reference level will be set at 10%.

11) Changes in the absolute values and percentages of bile acids at Week 4 and Week 12 during the treatment period relative to baseline (V2).
    In the FAS, changes in bile acids will be compared between treatment groups using the Student's t-test. FDR-correction using the Benjamini-Hochberg method will be applied, and the reference level will be set at 10%.
12) Changes in the absolute values and percentages for organic acids at Week 4 and Week 12 during the treatment period relative to baseline (V2).
   In the FAS, changes in organic acids between treatment groups will be compared using the Student's t-test. FDR-correction using the Benjamini-Hochberg method will be applied, and the reference level will be set at 10%.

13) Changes in the absolute values and percentages of amino acids relative to baseline (V2) at Week 4 and Week 12 during the treatment period.
   In the FAS, changes in amino acids will be compared between the treatment groups using the Student's t-test. FDR-correction using the Benjamini-Hochberg method will be applied, and the reference level will be set at 10%.

14) Change relative to baseline (V2) in C4 at Week 4 and Week 12.
   In the FAS, the change in C4 levels will be compared between the treatment groups using the Student's t-test.

16.3.3. Safety analysis
   The number and incidence rate of adverse events will be calculated in the SAS by event and severity. Similar tabulations will be conducted for adverse events and serious adverse events for which a causal relationship to the drug could not be ruled out. Vital signs and laboratory values will be summarized at each observation time point, and changes over time will be presented graphically.

16.4. Interim Analysis
   No interim analysis will be performed.

16.5. Procedures for handling missing, unused, and abnormal data
   In principle, imputation will not be performed when handling missing data during analysis. However, for discontinued cases, imputation of missing data will be considered when the patient has taken the study drug for at least one week. Detailed handling of unfilled data and abnormal data suspected to contain erroneous entries will be specified separately in the “Criteria for the elimination of cases.”

16.6. Procedures for changing the statistical analysis plan
   In this study, if there is a change from the original statistical analysis plan, the protocol will be revised and the nature of the change will be explained in the clinical study report.
17. Quality control and assurance

17.1. Source documents and the inspection thereof

The source documents for this study are as follows:

- Records concerning the subject's consent
- Medical records
- Examination records
- Study drug management table
- Records completed directly by subjects (patient diaries, questionnaires, etc.)
- Documents or records pertaining to the study
- Other

In this study, the supervising physicians and participating medical organizations will provide direct access to all clinical research-related records such as source documents during monitoring, audit, and investigation by the certified clinical research review board and regulatory agencies related to the clinical research.

17.2. Data management

Data management will be performed by data center personnel in this study. Queries will be generated to request for the verification and modification of outliers and abnormal values (confirmed by data monitoring) among data entered in the electronic Case Report Form.

After the data have been corrected by the data center, the finalized data will be provided to the statistical analysis manager. Details are specified in the data management plan.

17.3. Monitoring

To ensure the safety and protection of the human rights of subjects, this clinical study will be conducted in compliance with the latest implementation plans, study protocols, and Ministerial ordinances, and the principal investigator will prepare a separate "Monitoring Procedure" to verify that written consent has been obtained from subjects for the conduct of clinical study, and that the records, etc. are accurate to the source documents; the principal investigator will also carry out monitoring according to this procedure.

17.4. Audit

No audit will be conducted in this study.
18. Ethical matters

18.1 Rules to be observed

This study is considered as specified clinical research under the Clinical Research Act (Law No. 16, 2017) for the conduct of research, and will receive financial support from EA Pharmaceuticals Co., Ltd. and Mochida Pharmaceutical Co., Ltd., which are authorized pharmaceutical manufacturers. Therefore, this study will be conducted in compliance with clinical research methods and in accordance with ethical principles based on the Declaration of Helsinki.

18.2. Handling of personal information, etc.

Information that may identify subjects such as their names will not be transmitted to the participating medical organizations. Identification of and inquiries regarding test subjects will be handled using the case registration numbers issued at enrollment, subject identification codes, and sex information, so that third parties will not be able to identify the test subjects. Each participating medical institution will appropriately manage case registration numbers, etc. using correspondence tables. Prior to providing the case report form, laboratory data, specimens, etc. of the test subject to institutions outside the relevant medical institution, only those that are processed or anonymized (with respect to the identity of the corresponding test group) will be provided.

18.3. Expected benefits and disadvantages to subjects in accordance with research participation, etc.

18.3.1. Reasonably expected benefits

Participation in this study does not provide direct benefit to the subject. Research participation may contribute to future advances in healthcare.

18.3.2. Anticipated disadvantages

During the research period, the cost of examinations and medical treatment to be carried out in this study will be covered by financial support from EA Pharma Co., Ltd. and Mochida Pharmaceutical Co., Ltd., and the research drug will be provided by EA Pharma Co., Ltd. No financial burden will be placed on the study subjects. The research drug used in this study is approved for its indication and is covered by insurance for the target diseases of this study. In the placebo group, the symptoms may worsen due to discontinuation of laxatives, etc., from the observation period to the end of the treatment period, as detailed in “6.5.2.2. Prohibited concomitant drugs/therapies.” If a patient’s symptoms become difficult to control with the rescue drug, the investigator or sub-investigator will consider discontinuing the subject's participation in the research. In addition, the diseases, etc. that may occur in the subject will be evaluated according to the rationale in described in “12.4. Predictability”; if a disease, etc. occurs, the investigator or the research coordinating doctor will refer to “12.5. Measures to be taken in the event of a disease, etc.,” and take appropriate measures accordingly. There is a
possibility that the number of hospital visits will increase due to treatment for illness, and tests will be conducted.

18.4. Handling of study results (including incidental findings) for subjects

Although it is unlikely that this study will provide important information on the health of the test subject and the genetic characteristics that can be inherited by their offspring, if any information (including incidental findings) that significantly affects the health of the test subject is obtained through the tests performed as part of the study, the supervising physician or the sub-investigator will explain the information to the test subject and take appropriate measures, including applicable treatments and therapies. Results associated with participation in the study will be explained to them during treatment.

19. Cost burden and reward for examinees

During the study period, the costs related to examinations and medical care that will be provided in this study will be covered by financial support from EA Pharma Co., Ltd. and Mochida Pharmaceutical Co., Ltd., and the study drugs will be provided by EA Pharma Co., Ltd. There is no economic burden to the subjects.

In this study, subjects will be paid a cost reduction fee of ¥5000 via a Quo Card between the end of V2 (assigned subjects) and V5.

20. Compensation for health hazards

In the event of a health hazard to a test subject, appropriate treatment will be provided within the scope of the insurance coverage. Out-of-pocket payments for medical expenditures will be paid by the test subject. Clinical Research Liability Insurance shall be provided in preparation for compensation in the event of any liability for health damage caused by this study and in the event of death or sequel damage to the subject (1 to 2 grades of health damage). The provision for compensation is limited by certain conditions and may exclude or limit payment of compensation. Subjects are not eligible if they are negligent. In the event that a physician is negligent, the physician's liability insurance shall be applied.

21. Conflict of interest management related to the study, including funding sources for research

21.1. Funding sources and financial relationships

This study will be conducted with funding from EA Pharma Co., Ltd. and Mochida Pharmaceutical Co., Ltd. Study drugs used in research will be provided free of charge by EA Pharma Co., Ltd. Parties will enter into an investigator-initiated clinical research contract for the provision
of funding and drugs. EA Pharma Co., Ltd. and Mochida Pharmaceutical Co., Ltd. will prepare a study protocol through discussion with the principal investigator, but will not be involved in the decision-making regarding the conduct, analysis, and publication of this study.

21.2. Conflict of interest

21.2.1. Management of conflict of interest for the principal investigator and/or supervising physicians

The principal investigator will establish Conflict of Interest Control Standards, will confirm facts with administrators at participating medical organizations, and will prepare Conflict of Interest Control Plans. The principal investigator shall hear the opinions of the Accredited Clinical Research Review Board regarding conflict of interest management standards and conflict of interest management plans described in the implementation plan, and will apply the appropriate management measures.

21.2.2. Management of conflicts of interest for supervising physicians, etc.

In this study, when individuals report conflicts of interest, supervising physicians, sub-investigators, and statistical analysis managers will check factual relationships with administrators at participating medical organizations and obtain Conflict of Interest Confirmation Reports. The principal investigator will prepare a conflict-of-interest management plan based on the content of the Conflict of Interest Confirmation Reports, hear the opinions of the certified clinical research review board described in the implementation plan, and apply the appropriate management measures.

22. Control of compliance, changes, and non-compliance with the study protocol (deviations from the study protocol, etc.)

22.1. Compliance with the study protocol

The investigator or sub-investigator will not engage in actions that do not comply with the study protocol (i.e., deviations from or changes to the study protocol) without prior written approval based on prior agreement from the principal investigator and review by the certified clinical research review board as described in the protocol.

22.2. Changes to the study protocol

When a change is made, the principal investigator will submit the post-change implementation plan, protocol minor change notification, or protocol change notification to the certified clinical research review board for approval. After approval of the study implementation plan by administrators of the participating medical organizations, the protocol will be registered in the
jRCT, and the implementation plan will be submitted to the MHLW. When submissions are accepted and made publicly available on the jRCT, this will be notified to the certified clinical research review board and reported to the administrators of the participating medical organizations. In addition, each investigator will be informed, and the investigator will report to the manager of the participating medical organization.

22.3. Control of noncompliance (deviations from the study protocol, etc.)

Any study sub-investigators who become aware of noncompliance will report these instances to the supervising physicians, who will then promptly report to the supervisor of the participating medical organization, and inform the principal investigator. The principal investigator will inform all the investigators. In addition, the principal investigator and each research investigator will report to the manager of the relevant participating medical organization. The principal investigator and supervising physicians at the institution where the noncompliance has occurred shall consider appropriate measures to prevent recurrence.

If the principal investigator determines that the noncompliance that has occurred is particularly serious, he/she will promptly prepare a Unified Form 7 Serious Noncompliance Report and submit it to the accredited clinical research review committee to obtain its opinion.

If there is a concern that the principal investigator may not report the noncompliance to the appropriate report destination, the investigator may report it directly. Noncompliance will not be considered as serious in cases where the protocol was not followed for other medical reasons to avoid immediate hazard to the subject. Therefore, if such a course of action becomes unavoidable, it is not necessary to report it to the certified clinical research review board; however, even in such cases, a record of the noncompliance will need to be prepared.

23. Periodic report

23.1. Periodic reports to the accredited clinical research review board

The principal investigator will report the implementation status of the specified clinical research to the administrators of the participating medical organizations every year (within two months after the expiration of the period) starting from the date on which the implementation plan was submitted to the MHLW, and will then make periodic reports to the certified clinical research review boards described in the implementation plan. Reports on implementation status will contain the following information:

1. Number of participating subjects
2. Occurrence status and subsequent course of illness, etc.
3. Incidence of nonconformities and subsequent responses
4. Evaluation of safety and scientific validity
5. Items related to the involvement of drug marketing authorizations, etc. specified in the Conflict-of-Interest Control Standards

When the principal investigator reports to the certified clinical research review board, this information will also be promptly provided to the supervising physicians. The supervising physicians will then promptly report such information to the administrators of participating medical organizations.

23.2. Periodic report to the Minister of Health, Labor, and Welfare

The principal investigator will report the following information regarding the implementation status of specified clinical research to the MHLW within one month of the date on which the opinions of the accredited clinical research review board are put forth as described in the implementation plan.

1. Names of the committees listed in the implementation plan
2. Appropriateness of continuation of the specified clinical research by the committee
3. Number of subjects participating in specific clinical studies

24. Disclosure of study information and publication of results

24.1. Enrollment of studies

Prior to implementation, this study will be recorded (registered) in a database (jRCT = Japan Registry of Clinical Trials) prepared by the Ministry of Health, Labor, and Welfare. Any changes in the study protocol and progress in the research will be updated. When the study is completed, the results of the study will also be registered.

24.2. Publication of research results

The principal investigator will prepare the primary endpoint report or clinical study report and its outline. The time limit for preparation is one year after the completion of the period for collecting data on the primary endpoint or all endpoints.

When preparing the primary endpoint report or clinical study report and its outline, the principal investigator will hear the opinions of the certified clinical research review board as described in the protocol and submit the same to the administrators of the participating medical organizations without delay; the principal investigator will also record (register) the summary of the primary endpoint report or clinical study report in the jRCT. “Without delay” is defined as “no later than one month from the date on which the Commission expresses its opinion”. Upon submission to the administrators of the participating medical organizations, the principal investigator will inform the
other investigators, and the other investigators will promptly report this information to the manager of the other participating medical organizations.

24.3. Promulgation via academic societies, etc.

The results obtained from this study will be promptly promulgated via a conference presentation or an article publication. During the promulgation, necessary steps will be taken to protect the rights of the subjects and their relatives, and the rights of researchers and their relatives. Society presenters and the first author of the article will decide in consultation.

25. Attribution of study outcomes (intellectual property rights)

If an invention is made in the course of the conduct of this study, the corresponding intellectual property rights should be handled in consultation with EA Pharma Co., Ltd. and Mochida Pharmaceutical Co., Ltd.. However, the intellectual property rights related to the study drug are attributed to EA Pharma Co., Ltd.

26. System for conducting research

See Appendix 1.

27. Participating centers and institutional investigators

See Appendix 2.

28. References

[13] Notification No. 821-1 of the Health and Medical Safety Bureau dated August 21, 2018 Regarding partial amendments to precautions associated with changes to indications, etc. under the Pharmaceuticals and Medical Devices Law.
[15] Guideline on the evaluation of medicinal products for the treatment of chronic constipation (including opioid-induced constipation) and for bowel cleansing. European Medicines Agency

29. Appendix

Attachment 1: Implementation system for the study
Attachment 2: Participating centers and institutional research investigators
Patient diary
Questionnaire: PAC-QOL (Japanese version)
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 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. 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 prusenide 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 10 mg, 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 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 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>V1 Registration</th>
<th>V2 Randomisation</th>
<th>V3</th>
<th>V4</th>
<th>V5 EOT Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Window</td>
<td>V2-4 weeks after registration</td>
<td>± 7 days</td>
<td>± 7 days</td>
<td>± 7 days</td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Vital signs/height and weight</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Blood test</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Registration</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Confirmation of administration start criteria allocation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Blood and stool collection for exploratory research</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Providing drugs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Checking the medication status</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Review concomitant medications</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Review rescue drugs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Review adverse events</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Questionnaire/Review patient diary</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Patient diary confirmation</td>
<td>-</td>
<td>-</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 prussenide 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.
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, aldioxa, 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></td>
</tr>
<tr>
<td>Drugs for irritable bowel syndrome (e.g., ramosetron hydrochloride, calcium polycarbophil, trimebutine maleate)</td>
<td>From observation period to the end of the treatment period</td>
</tr>
<tr>
<td>5-HT3 antiemetic</td>
<td></td>
</tr>
<tr>
<td>Gastropokinetic 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】
<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.
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.niph.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 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, 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, 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. 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

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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.niph.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 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.
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. 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.

☐ 8. Matters concerning the protection of the personal information of the subjects of the Specified Clinical Research, etc.

☐ 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, audits, etc., and if so, what personal information will be disclosed in such inspection.

☐ 10. The 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 specified 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)