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)

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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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<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
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<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
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<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>
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<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>
</tr>
</tbody>
</table>
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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<tr>
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</thead>
<tbody>
<tr>
<td>Study Protocol No.</td>
<td>TANK-27</td>
</tr>
<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>
<tr>
<td>Target number of test subjects</td>
<td>Number of patients included in the analysis: 100</td>
</tr>
</tbody>
</table>

### 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)**
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>
<th>AJG533 (elobixibat) 10 mg group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of administration, observation, and duration of administration</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Evaluation Items</td>
<td><strong>Efficacy</strong></td>
<td></td>
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<td></td>
<td>Primary endpoint:</td>
<td></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>
<td></td>
</tr>
<tr>
<td></td>
<td>*SBMs without feeling of residual stool</td>
<td></td>
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<tr>
<td></td>
<td>Secondary endpoints:</td>
<td></td>
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<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>
<td></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>
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<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>
<td></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>
<td></td>
</tr>
<tr>
<td></td>
<td>· Percentage of responders *** as seen in the number of CSBMs during treatment (12 weeks)</td>
<td></td>
</tr>
</tbody>
</table>
Responder Definition: at least three CSBMs 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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Department of Palliative Medicine, Yokohama City University Hospital
TEL: 045-787-2800 (representative)
Research office: Yokohama City University Hospital
Rules to be observed

All persons involved in this study will adhere to and understand the content of the World Medical Association Declaration of Helsinki and the Law, Enforcement Regulations, and General Notifications that all medical research involving human subjects should comply with in their performance of clinical research.

**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 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 diet, life, 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 life 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 tables 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.

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 Pursennid 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 (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

```
Informed consent
Eligibility confirmation

Registration

Confirmation of administration start criteria

Randomization

EXB 10mg
QD
N=50

PBO
QD
N=50

12-week follow-up
```

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

20
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 Pursefri tablet 12 mg/2 tablets once) may be used in the following conditions:

- Bisacodyl suppository 10 mg/1 tablet once or Pursefri 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 Pursefri 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 Pursefri 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)
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-HT\textsubscript{3} 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 cholestamide
- 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>Informed consent</th>
<th>Observation period</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>V1 Registration</td>
<td>V2 Randomisation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V3 Randomisation</td>
<td>V4 Week 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V5 Week 8</td>
<td>V5/End Discontinuation</td>
</tr>
</tbody>
</table>

- **Informed consent Window**: 2–4 weeks after registration ± 7 days ± 7 days ± 7 days

<table>
<thead>
<tr>
<th>Informed consent</th>
<th>Observation period</th>
<th>Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visitor consent</td>
<td>V1 Registration</td>
<td>V2 Randomisation</td>
</tr>
<tr>
<td></td>
<td>V3 Randomisation</td>
<td>V4 Week 4</td>
</tr>
<tr>
<td></td>
<td>V5 Week 8</td>
<td>V5/End Discontinuation</td>
</tr>
</tbody>
</table>

- **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) Hematology: 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-l, 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 responders * as per the number of CSBMs during the treatment period (12 weeks)
    Defining * 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 °C.
    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>≥5%</th>
<th>&lt;1-5%</th>
<th>&lt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver</strong></td>
<td>Liver function test abnormal (ALT (GPT) increase, AST (GOT) increase).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychoneurological</strong></td>
<td></td>
<td>Headache, dizziness</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td>Hot flushes</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></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><strong>Hypersensitivity</strong></td>
<td></td>
<td></td>
<td>Urticaria, rash</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td>Elevated eosinophil counts, anemia, Elevated vitamin E levels</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></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>Infections</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>
<tr>
<td>Non-infectious diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Death</td>
<td></td>
<td>Not applicable</td>
<td>15 days</td>
</tr>
<tr>
<td>2. Diseases etc. requiring admission to a medical institution or prolonged hospital stay for treatment</td>
<td>Other, cannot be predicted 2)</td>
<td>15 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other than the above</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Disorders</td>
<td>Other, cannot be predicted</td>
<td>15 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other than the above</td>
<td></td>
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<tr>
<td>4. Diseases that may lead to death or disability</td>
<td>Other, cannot be predicted</td>
<td>15 days</td>
<td></td>
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<td></td>
<td>Other than the above</td>
<td></td>
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<tr>
<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>
<td></td>
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<td></td>
<td>Other than the above</td>
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<tr>
<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>
<td></td>
</tr>
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<td></td>
<td>Other than the above</td>
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<tr>
<td>1. Death</td>
<td></td>
<td>Not applicable</td>
<td>15 days</td>
</tr>
<tr>
<td>2. Diseases etc. requiring admission to a medical institution or prolonged hospital stay for treatment</td>
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<td>15 days</td>
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<td></td>
<td>Other than the above</td>
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</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 subject 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 CSBMs 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 CSBMs during treatment (12 weeks). The percentage of responders with reference to CSBMs 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)