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A multicentre, placebo-controlled, randomised, double-blind, parallel-group study investigating the efficacy and safety of elobixibat, an ileal bile acid transporter inhibitor, in patients with Parkinson's disease with chronic constipation (CONST-PD): The protocol

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ABSTRACT

Introduction

Chronic constipation can worsen the quality of life (QOL) of patients with Parkinson's disease (PD). Elobixibat, an ileal bile acid transporter inhibitor, is known to be a useful laxative, but whether it has an effect on chronic constipation in PD patients remains unclear. Therefore, we have planned a placebo-controlled, randomised, double-blind study to investigate the efficacy and safety of elobixibat in PD patients with chronic constipation.

Methods and analysis

The study will consist of 2-week observation and 4-week treatment periods. Patients diagnosed with clinically established PD will record the status of spontaneous bowel movements and use of rescue medications/concomitant medications in a Bowel Movement Diary from the start of the observation period at Visit 1 (Week -2). At Visit 2 (Week 0), patients will be assessed for final registration based on the Diary records and physical examinations, and then allocated to either the elobixibat or placebo group. Records of daily intake of the investigational drug will be included in the Diary. Patients will undergo laboratory tests and answer constipation-related, PD-related, and QOL-related questionnaires at Visit 2 and Visit 4 (Week 4). Subjective symptoms and objective findings will be collected at Visits 2, 3 (Week 2), and 4. Since patients' motor function might be improved by treatment of constipation, the use of dopamine preparations will also be monitored. Bowel movement data and other parameters will be compared between the elobixibat and placebo groups.

Safety information will be collected as adverse events, while specifically focusing on

those occurring in association with study conduct.

Ethics and dissemination

This study will be conducted in accordance with the Helsinki declaration, the Clinical Trials Act of the Japan Ministry of Health, Labour and Welfare, and related laws and regulations. All patient data will be anonymized to protect privacy and used only for the study purpose.

Registration number of this study: JPRN-jRCTs031200172 (Japan Primary Registries Network)

Keywords

Parkinson's disease, Motility disorders, Clinical trials

Strengths and limitations of the study

- This study will explore the efficacy and safety of elobixibat versus placebo in PD patients with chronic constipation in a randomised, double-blind manner.
- Given that there is evidence that probiotic/prebiotic fibre, lubiprostone, and macrogol improve chronic constipation in PD patients, this study is expected to provide further evidence to expand treatment options to improve the disease condition and, thereby, the patients' quality of life.
- Because of the short study period (4-week administration), the long-term efficacy and safety of elobixibat may not be clarified.
- Diary data might have limited credibility because they are based on the patients' subjective responses.

INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative disorders. Whereas PD is commonly considered a movement disorder, patients with PD have many difficulties with non-motor symptoms, such as dementia, anxiety, sleep disturbance, and autonomic dysfunction.[1] Chronic constipation is one of the common digestive complications experienced by PD patients even before or at an early stage of disease progression, with its frequency varying from 7% to 70% depending on the definition.[2-6] Since long-lasting constipation may decrease quality of life (QOL) and be occasionally accompanied by life-threatening intestinal perforation and/or megacolon syndrome, it should be appropriately controlled.[7,8]

Multiple types of laxatives are conventionally available for the treatment of chronic constipation, including bulk-forming agents such as carmellose sodium and dioctyl sodium sulfosuccinate, stimulants such as sennoside and sodium picosulphate hydrate, and osmotic agents such as cathartic salts (magnesium oxide and magnesium sulphate). While stimulants and cathartic salts have been widely used, stimulants may cause intractable constipation via drug resistance if used consecutively for a long duration, and magnesium oxide may cause hypermagnesemia in elderly patients and patients with kidney malfunction.[9]

Recently, in addition to existing osmotic agents (macrogol 4000 often in combination with electrolytes, movicol, lactulose), new classes of laxatives have been developed for chronic constipation, including epithelial function transformation drugs (lubiprostone, linaclotide) and an ileal bile acid transporter (IBAT) inhibitor (elobixibat).

However, the evidence for the effectiveness of laxatives either conventional or recently developed for the treatment of chronic constipation in PD patients is not extensive, except for macrogol and lubiprostone, a chloride channel-2 activator, which have been shown to be significantly efficacious over placebo in improving bowel movement frequency.[10, 11] Although probiotics and prebiotic fibre were also proposed to be useful for the treatment of PD-related constipation,[12, 13] more evidence for different classes of laxatives is needed to expand therapeutic options for chronic constipation in PD patients.

Elobixibat is an inhibitor of IBAT, which is expressed in the distal ileum. Bile acids escape the reabsorption process via the action of this drug and then enter the large intestinal lumen.[14] The increased levels of bile acids may lead to an influx of water and electrolytes into the lumen, inducing colonic high-amplitude propagated contractions (HAPCs). Elobixibat is thus expected to be a novel option for the treatment of chronic constipation on the basis of its mode of action being totally different from

those of the other existing laxatives.[15, 16]

We are planning to conduct a study to examine the efficacy and safety of elobixibat in PD patients with chronic constipation. The superiority of elobixibat over placebo will be explored in a randomized, double-blind, comparative study during 4-week daily administration of the drug to eligible patients. The drug will also be evaluated for its safety and potential impact on the underlying PD condition. This study was approved by the Ethics Committee of the Juntendo University School of Medicine (J20-009). The study methodology is detailed in this article.

METHODS AND ANALYSIS

The objective of this study is to explore a novel therapeutic option for chronic constipation in PD patients.

Primary endpoints

The weekly frequency of spontaneous bowel movements with no assistance from rescue therapies such as bisacodyl suppositories, enema, disimpaction, etc. (see below) will be recorded during each 7-day segment of the treatment period (Week 0-1 up to Week 3-4; see Figure 1). Bowel movements observed within 24 hours of suppository use will not

be counted. Changes in the frequency at Visit 4 (Week 4) from baseline (Visit 2/Week 0; see Figure 1) will be compared between the elobixibat group and the placebo group.

Secondary endpoints

Weekly changes from baseline in the frequency of spontaneous bowel movements and complete spontaneous bowel movements (i.e., no sensation of incomplete evacuation) will be assessed throughout the treatment period (Visit 4/Week 4; Figure 1). Changes from baseline in stool form will also be assessed up to Week 4 using the Bristol Scale.[17]

Use of rescue medication and questionnaire surveys using the Japanese version of Patient Assessment of Constipation Quality of Life (JPAC-QOL),[18] Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS),[19] Parkinson's Disease Questionnaire-39 (PDQ-39),[20] and Euro-Qol 5 dimension – 5 level (EQ-5D-5L)[21,22] will be assessed. The use of dopamine preparations will also be monitored, since the effectiveness of elobixibat in improving constipation via increased levels of intestinal bile acids may also improve small intestinal absorption of the anti-Parkinsonian medications.

Subgroup analyses will be further performed for these endpoints by patient background

and dose of investigational drug.

Overall study design

This study is designed as a randomised, double-blind, placebo-controlled, parallel-group study at 2 academic centres (Juntendo University Urayasu Hospital, and Juntendo University Nerima Hospital), in which PD patients with chronic constipation will pre-prandially receive elobixibat (Goofice®; EA Pharma Co., Ltd., Tokyo, Japan) or its indistinguishable matched placebo once daily for four weeks, and the frequency of spontaneous bowel movements will be compared between the patients receiving either elobixibat or placebo. Safety information, including adverse events (AEs) and discontinuation and interruption of the investigational drugs, will also be collected.

The study will consist of two periods, the observation period and the treatment period. It will be conducted from October 26, 2020 (date of the first announcement in the Japan Registry of Clinical Trials; jRCT) through September 30, 2022. As seen in Figure 1, we plan two steps for patient registration, temporary and final. At Week -2 (Visit 1) of the observation period, PD patients will be provided with the detailed information about the study. After providing written, informed consent for study participation, they will be temporarily registered based on the patient definitions (see below). Following the

observation period, the patients will be further assessed for study participation at Week 0 (Visit 2). Once none of the exclusion criteria are confirmed to be applicable, the patients will be finally registered and assigned to either the elobixibat group or the placebo group in a double-blind manner (Figure 1). The eligible patients will visit their clinical sites twice more (Visit 3 at Week 2 and Visit 4 at Week 4) during the 4-week treatment period.

A Bowel Movement Diary will be provided at Week -2 (Visit 1, see below) to each patient, once temporarily registered. The patient will record drug use, bowel movements, etc. in the Diary daily throughout the study period.

Patient definitions

Patients will be diagnosed as having PD in reference to the diagnostic criteria defined by the International Parkinson and Movement Disorder Society (MDS)[23] and must be in stages 1 to 4 on the Hoehn and Yahr scale.[24] The diagnosis of chronic constipation will be made referring to the Rome IV-defined criteria.[25,26] Outpatients aged ≥20 years at the time of informed consent must have two or more of the following symptoms related to spontaneous bowel movements from at least 6 months before consent: i) <3 spontaneous bowel movements per week; ii) straining frequency >25% of defecations;

iii) frequency of lumpy or hard stools >25% of defecations; and iv) sensation of incomplete evacuation >25% of defecations. Patients who meet these criteria will be temporarily registered, once written, informed consent is provided (Figure 1).

A PD patient will be excluded at temporary registration if he/she: has (or is suspected to have) organic constipation or dyschezia; is unable to use a rescue medication (bisacodyl 10 mg suppositories; Teleminsoft Suppositories® 10 mg, Cox Japan, Tokyo, Japan); currently has serious kidney dysfunction (creatinine ≥2.00 mg/dL), serious hepatic dysfunction (total bilirubin ≥3.0 mg/dL, or AST or ALT ≥100 U/L), or serious cardiac dysfunction; has malignant tumour(s); has a history of hypersensitivity to elobixibat; is taking bile acid preparations (ursodeoxycholic acid, chenodeoxycholic acid), aluminium-containing preparations (sucralfate hydrate, aldioxa, etc.), cholestyramine, colestimide, digoxin, dabigatran etexilate mesylate, or midazolam; has a Mini–Mental State Examination (MMSE) score[27] ≤26; or is considered ineligible by the investigator or sub-investigator, hereinafter termed (sub)investigator, for study participation because of safety concerns, poor protocol compliance, etc. Female patients will also be excluded if they are pregnant, breastfeeding, or expecting pregnancy during the study period.

Patient exclusion is further scheduled at the final registration if one of the following cases applies to a patient during the 2-week observation period: use of the rescue medication (bisacodyl 10 mg suppositories) ≥5 times; use of the rescue medication within 72 hours post-bowel movement; experience of spontaneous bowel movement with mushy or watery stool according to Bristol Stool Form Scale (BSFS) type 6 or 7;[17] or use of prohibited medications/therapies (see below).

Study procedures and schedule

Registration of study patients and their allocation to the investigational drug will be performed via an internet-mediated Interactive Web Response System (IWRS). The (sub)investigator (or study-assigned coordinator) will access the specific website for patient registration and allocation using a specific ID and password and complete the necessary information about each anonymized patient. Investigational drug allocation will be instantly presented for each patient following eligibility judgment. Drug allocation will be based on a stratified, permuted block method with sex as an allocation factor.

The schedule of this study is shown in Figure 2.

The (sub)investigator will give detailed explanations of this study to each PD patient

who meets the inclusion criteria but not the exclusion criteria at Visit 1 and then obtain the patient's written, informed consent on a free will basis. The patient will be informed that he/she may withdraw his/her consent for any reason and at any time during the study period. The (sub)investigator will give the eligible patient a temporary identification code and enter the patient's background in the Eligibility for Temporary Registration form of the electronic Case Report Form (eCRF; see Figures 1 and 2).

The Bowel Movement Diary and rescue medication (bisacodyl 10 mg suppositories) will be provided to each patient at temporary registration. The (sub)investigator will instruct each patient how to complete the required items in the Diary.

At Visit 2, the (sub)investigator will judge the eligibility of each patient for final registration referring to the exclusion criteria (see above) and enter the background of qualified patients in the Eligibility for Final Registration form of the eCRF. Once the patient's eligibility is confirmed, a final identification code will be assigned to the patient, who will be then allocated randomly to treatment group. The (sub)investigator will check the final identification code and the allocated investigational drug number for each qualified patient on the IWRS screen. The specifically numbered drug will be provided to the patient by the (sub)investigator at Visit 2 and Visit 3 for 2 weeks each time (3 tablets x 14 days), as described below.

The patient will start the 4-week treatment period with once-daily, preprandial intake of 2 tablets of investigational drug (elobixibat 10 mg) or its placebo. One tablet may be added on the next day if no spontaneous bowel movement is observed during the next 24 hours. If excessive effectiveness or discomfort appears, the dosage may be decreased at the direction of the (sub)investigator or the patient's judgment. Dose augmentation from 1 tablet to 3 tablets will not be allowed. Interruption of the investigational drug due to the occurrence of an AE may be allowed at the direction of the (sub)investigator or the patient's judgment, but as-needed intake of the drug based on bowel movement status will not be acceptable. The drug may be restarted at the dose taken immediately before interruption or at a lower dose. Inappropriately long (≥7 consecutive days) or frequent (≥3 days per week during 2 consecutive weeks) interruption of the drug may lead to discontinuation of the patient from the study at the (sub)investigator's discretion.

Rescue and concomitant medications/therapies

Since this study is primarily planned to explore the efficacy and safety of elobixibat as a laxative in PD patients, concomitant medications will be used throughout the study period for parkinsonism except for Duodopa® pump therapy (Abbvie Inc., North Chicago, IL, USA) with levodopa/carbidopa hydrate intestinal gel. Bisacodyl 10 mg

suppositories may be used once to twice daily as a rescue medication when no bowel movement is observed for 72 or more consecutive hours, unless emergency use is required.

Because of potential effects on the study results and/or interpretation thereof, use of the following drugs or therapies as concomitant medications will be prohibited: laxatives other than elobixibat such as magnesium hydroxide, sodium picosulphate, sennosides, lubiprostone, linaclotide, polyethylene glycol (macrogol 4000), etc.; oriental medicines for constipation (daiokanzoto extract, choijokito extract, daisaikoto extract, etc.); medicines indicated for irritable bowel syndrome (ramosetron hydrochloride, polycarbophil calcium, trimebutine maleate, etc.); supplements or over-the-counter drugs to improve the constipated condition; enema or intestinal lavage; lavage solution for colonoscopy; drugs listed in the Precaution section of the package insert of elobixibat (Goofice® 5 mg tablets) as "with caution for concomitant use" (bile acid preparations such as ursodeoxycholic acid and chenodeoxycholic acid, aluminium-containing antacids such as sucralfate hydrate, aldioxa, etc., cholestyramine, cholestimid, digoxin, dabigatran etexylate methanesulfonate, and midazolam; other medicines or investigational drugs being used in clinical trials; non-internal therapy for constipation such as biofeedback therapy; disimpaction; and Duodopa® pump therapy.

Discontinuation of the study

Participation of a recruited patient will be discontinued if any of the following conditions is met: judged difficult to continue due to the onset of an AE; ineligibility confirmed after study initiation; lost to follow-up; confirmed or suspected pregnancy; voluntary withdrawal; repeated protocol violations; or any other reason for which the (sub)investigator judges that discontinuation would be necessary.

All study procedures will be discontinued if any of the following conditions is met: the Institutional Review Board of Juntendo University Hospital determines that the study should be discontinued; the appearance of safety concerns with potential impact on study progress; appearance of incidents or information that may potentially lead to impairment of ethical or scientific validity of the study; or appearance of any other incidents or information that may potentially lead to impairment of appropriateness of study conduct and/or reliability of study results.

Observations and measurements

Patient background, medical history and complications, and data of physical examinations will be collected at Visit 1 (Figure 2). On final judgment regarding study

registration at Visit 2, subjective symptoms and objective findings, medical history and complications, physical examinations, and vital signs will be recorded for the eligible patients. Subjective symptoms and objective findings will be collected twice more at Visits 3 and 4. Physical examinations and vital signs will also be recorded at Visit 4. The JPAC-QOL,[18] MDS-UPDRS,[19] PDQ-39,[20] and EQ-5D-5L21,[22] surveys and laboratory measurements (haematology and blood chemistry) will be recorded at Visits 2 and 4 (Figure 2).

Each patient will receive a Bowel Movement Diary at Visit 1 and will then record daily the status of bowel movements (date, stool hardness based on the Bristol scale,[17] and sensation of incomplete evacuation), use of rescue medication (date, dose of bisacodyl suppositories) and concomitant medication (drugs for treatment of PD-related motor symptoms; date, drug name, dose), and treatment with non-investigational drugs and/or therapy for constipation. If the patient enters the treatment period, he/she will continue to record those items and also record daily use of the investigational drug (elobixibat or placebo; date and dose, i.e. number of tablets taken) in the Diary starting at Visit 2 up to the end of study (Visit 4). Discontinuation, if it occurs, should also be recorded in the Diary with its date and reason.

Safety information

This study will specifically focus on AEs that are suspected to have occurred in association with study conduct and include any of study conduct-associated events, impairments, deaths, infections, laboratory abnormalities, and symptoms.

The (sub)investigator will examine the patient for AEs throughout the study period (Figure 2) and upon finding an event, record in the patient's eCRF its: name; onset date; severity (mild, moderate, or severe); seriousness (non-serious or serious); defined category of seriousness (death, life-threatening, hospitalization-initial or prolonged, disability or permanent damage, an event potentially leading to disability or permanent damage, ill condition judged as serious in reference to the aforementioned categories, or congenital anomaly or birth defect); predictability (known or unknown); action taken regarding the investigational drug (continuation, interruption, or discontinuation); outcome (recovered, improving, not recovered, recovered with sequelae, died, or unknown); date of outcome; causal relationship with use of the investigational drug ('not related' or grades other than 'not related'; suspected factor(s) other than the investigational drug should be recorded if judged 'not related').

Study population and statistical analysis

Based on the efficacy assessment of elobixibat vs. placebo in phase 2 and phase 3 clinical trials conducted in Japanese patients with chronic constipation,[28-30] we estimated a sample size of 40 patients for each group for 90% detection power at a two-sided significance level of 5%. Assuming a dropout rate of 20%, we plan to recruit 100 PD patients with chronic constipation in this study.

The full analysis set (FAS) is defined as the randomised population receiving at least one dose of the investigational drug with any measurement with regard to efficacy assessment. To ensure the robustness of study results, we also define a per-protocol set (PPS) as the population after the patients are excluded from the FAS due to any of the following reasons: any of the inclusion criteria inapplicable or any of the exclusion criteria applicable; a patient receiving the investigational drug with a non-allocated drug number; a patient receiving prohibited concomitant medications or therapies; a patient deemed to be inappropriate for study participation due to low drug compliance, lost to follow-up, lack of measurements, etc. The safety analysis set is defined as a population receiving at least one dose of the investigational drug after randomization.

Continuous variables and categorical variables will be presented as means±standard deviation (SD) and as frequencies and percentages, respectively. Summary statistics may include medians and quartiles, as appropriate. Comparisons will be made for

primary outcomes between the elobixibat group and the placebo group by analysis of covariance (ANCOVA) using baseline values and sex as covariates. Adjusted means with 95% confidence intervals and p values will be presented at a two-sided significance level of 5%. Within-group variations will be assessed by paired *t*-tests. Missing values will be imputed by the last observation carried forward (LOCF) method. Safety data will be shown as frequencies and percentages by group and individual event.

PATIENT AND PUBLIC INVOLVEMENT

No formal patient advisory committee was established, and there was no patient or public involvement in the design and planning of the study.

ETHICS AND DISSEMINATION

This study will be conducted according to the protocol that has been prepared in accordance with the Helsinki Declaration, Clinical Trials Act of the Japan Ministry of Health, Labour and Welfare, and related laws and regulations. Each study patient will be anonymously identified by a specific identification code and hence protected against privacy invasion. The information and data of each patient will be used exclusively for the study purpose and will never be disseminated outside the study.

As a coordinating centre, SRD Co., Ltd. will share necessary information related to this study at the participating medical organizations in this study, conduct operations aimed at facilitating this study, and provide support to investigators.

Data management and monitoring are conducted by Juntendo Clinical Research and Trial Center, Juntendo University Hospital. Details are specified in the Data Management Plan and Monitoring Plan.

If a serious health hazard arises due to participation in this study, coverage benefits can be received from insurance carried by a principal investigator, provided, however, that compensation may be reduced or not compensated if it is proven that the health hazard was caused by the research subject's own wilful act or gross negligence. In addition, if there is no causal relationship between the newly occurring health hazard and the deterioration of the originally affected disease, it is not covered by compensation. After completion of the study by each research subject, the investigators will make efforts to provide the best medical care obtained from the results of the research.

DISCUSSION AND DISSEMINATION

PD treatment is usually focused on the amelioration of movement dysfunction. However, patients with PD have many non-motor symptoms, especially autonomic

dysfunction. Chronic constipation has been considered one of the troublesome symptoms affecting the QOL of PD patients, and it may even be life-threatening.

Although fermented milk products containing probiotics and prebiotic fibres may have a favourable effect on PD-related constipation, they will not be available as laxatives.

Although multiple classes of laxatives are available, there is little evidence supporting their use for PD-related constipation. An evidence-based medicine review[1] recommends only three drugs/foods for PD-related constipation, including macrogol, lubiprostone, and probiotics/prebiotic fibres. Two laxatives are considered "likely efficacious" and "possibly useful" for the treatment of constipation in PD patients based on the quality of randomised, controlled trials. We believe the randomised, clinical study proposed here will be useful for expanding treatment options for PD-related constipation in an evidence-based manner.

The study findings will be presented at relevant conferences and published in a peer-reviewed journal.

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Authors' Contributions

TH, GO, and NH were involved in conception and trial design. TH was involved in drafting of the article. TH, GO, YS, KO, NN, JF, RN, NK, TT, YO, SS, KN, HE, AF, AN, MK, DT, TO, HTA, HK, SN, and NH were involved in critical revision of the article for important intellectual content. All the authors were involved in final approval of the article. NY provided statistical expertise.

Data availability statement

Data are available on reasonable request (TH; thatano@juntendo.ac.jp).

Funding

This study will be funded by EA Pharma Co., Ltd. (Tokyo) and Mochida Pharmaceutical Co., Ltd. (Tokyo) (grant number: N/A). The two companies also provide clinical supplies, the Bowel Movement Diary, and other products necessary for

study conduct. It should be noted that the two companies and their employees will never be involved in any study procedures including collection, analysis or interpretation of data, ensuring (sub)investigators will be completely independent of the funders throughout study conduct.

Competing interests

There are no competing interests.

FIGURE LEGENDS

Figure 1 Study outline

Washout: previous medications except for anti-Parkinsonian medications will be washed out during the observation period.

Consent: written, informed consent

Exam.: physical examinations

Test: laboratory tests

Eligibility: eligibility confirmed for study participation

Alloc.: patient allocation to either treatment with elobixibat or with placebo

Prescrip.: prescription of the investigational medication according to patient allocation

Drug retrieval: unused/remaining investigational medications will be retrieved.

Figure 2 Study schedule

[a]: Allowance denotes the time window allowed relative to the date of Visit 1 for Visit 2 and Visit 2 for Visits 3 and 4.

[b]: Temporary registration for study participation

[c]: Final registration for study participation

Figure 1

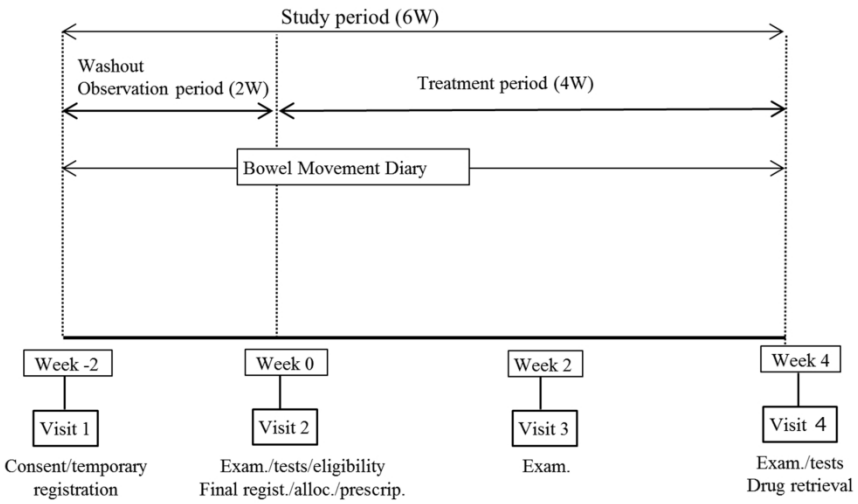

Figure 1 Study outline

253x190mm (300 x 300 DPI)

Figure 2

		Observation period	Administration start	Treatment period	
Visit		Visit 1	Visit 2	Visit 3	Visit 4
Date (Allowance[a])		14 days prior to Visit 2	Day 1 (≤ 5 days post-Visit 2)	Day 15 post Visit 2 (≤± 7 days))	Day 29 post Visit 2 (≤ 7 days) or discontinuation
Informed consent		○			
Eligibility confirmation		○ (Temp. regist.[b])	○ (Final regist.[c])		
Physical examinations	Patient background	○			
	Subjective symptoms/objective findings		○	○	○
	History/complications	○	○		
	Physical examinations	○	○		○
	Vital signs (blood pressure/pulse rate)		○		○
Bowel Movement Diary	Use of investigational medication		◄———	———	———►
	Use of rescue/concomitant medication	◄———	———	———	———►
	Bowel movement	◄———	———	———	———►
	Other therapy for constipation	◄———	———	———	———►
Adverse events		◄———	———	———	———►
JPAC-QOL			○		○
MDS-UPDRS			○		○
PDQ-39			○		○
EQ-5D			○		○
Laboratory tests	Haematology		○		○
	Blood chemistry		○		○

Figure 2 Study schedule

253x190mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	34
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 34
	5b	Name and contact information for the trial sponsor	34
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6-8
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	22

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-8
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	6-8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-8, 10, 11
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11, 13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10, 11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15-17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13-15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-17
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	17, 18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig. 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19-21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	19-21
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13-15
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13-15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13-15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13-15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	19-21
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	19-21

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	22
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8, 9, 19-21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8, 9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19-21
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10-13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	34, 35
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21, 22
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10-13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____15____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____NA____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__17, 21, 22___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__34, 35_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__34_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___22_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___26_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____34_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____NA_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol: A multicentre, placebo-controlled, randomised, double-blind, parallel-group study investigating the efficacy and safety of elobixibat, an ileal bile acid transporter inhibitor, in patients with Parkinson's disease with chronic constipation (CONST-PD)

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Parkinson-s disease < NEUROLOGY, Motility disorders < GASTROENTEROLOGY, Clinical trials < THERAPEUTICS

Protocol: A multicentre, placebo-controlled, randomised, double-blind, parallel-group study investigating the efficacy and safety of elobixibat, an ileal bile acid transporter inhibitor, in patients with Parkinson's disease with chronic constipation (CONST-PD)

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ABSTRACT

Introduction

Chronic constipation can worsen the quality of life (QOL) of Parkinson's disease (PD) patients. Elobixibat, an ileal bile acid transporter inhibitor, is known to be a useful laxative, but its effect on chronic constipation in PD patients remains unclear. Therefore, we have planned a placebo-controlled, randomised, double-blind study to investigate the efficacy and safety of elobixibat in PD patients with chronic constipation.

Methods and analysis

The study will consist of 2-week observation and 4-week treatment periods. Patients diagnosed with clinically established PD will record the status of spontaneous bowel movements and use of rescue medications/concomitant medications in a Bowel Movement Diary from the start of the observation period at Visit 1 (Week -2). At Visit 2 (Week 0), patients will be assessed for final registration based on the Diary records and physical examinations, and allocated to either the elobixibat or placebo group. Daily intake of the investigational drug will be recorded in the Diary. Patients will undergo laboratory tests and answer constipation-related, PD-related, and QOL-related questionnaires at Visit 2 and Visit 4 (Week 4). Subjective symptoms and objective findings will be collected at Visits 2, 3 (Week 2), and 4. Since patients' motor function might be improved by treatment of constipation, the use of dopamine preparations will also be monitored. Bowel movement data and other parameters will be compared between the groups.

Safety information will be collected as adverse events, specifically focusing on those occurring in association with study conduct.

Ethics and dissemination

This study will be conducted in accordance with the Helsinki Declaration, the Clinical Trials Act of the Japan Ministry of Health, Labour and Welfare, and related laws and regulations. Patient data will be anonymized to protect privacy and used only for the study purpose. The present study was approved by the Juntendo University Certified Review Board.

Registration number of this study: JPRN-jRCTs031200172 (Japan Primary Registries Network)

Keywords

Parkinson's disease, Motility disorders, Clinical trials

Strengths and limitations of the study

- Given that there is evidence that probiotic/prebiotic fibre, lubiprostone, and macrogol improve chronic constipation in Parkinson's disease (PD) patients, this study is expected to provide further evidence to expand treatment options in PD patients, using a different anti-constipation drug with a different mode of action.
- Elobixibat, an ileal bile acid transporter inhibitor and a new class of laxative, may improve constipation and, thereby, quality of life in PD patients.
- Because of the short study period (4-week administration), the long-term efficacy and safety of elobixibat may not be clarified.
- Bowel Movement Diary data might have limited credibility because they are based on the patients' subjective responses.

INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative disorders. Whereas PD is commonly considered a movement disorder, patients with PD have many difficulties with non-motor symptoms, such as dementia, anxiety, sleep disturbance, and autonomic dysfunction.[1] Chronic constipation is one of the common digestive complications experienced by PD patients even before or at an early stage of disease progression, with its frequency varying from 7% to 70% depending on the definition.[2-6] Since long-lasting constipation may decrease quality of life (QOL) and be occasionally accompanied by life-threatening intestinal perforation and/or megacolon syndrome, it should be appropriately controlled.[7,8]

Multiple types of laxatives are conventionally available for the treatment of chronic constipation, including bulk-forming agents such as carmellose sodium and dioctyl sodium sulfosuccinate, stimulants such as sennoside and sodium picosulphate hydrate, and osmotic agents such as cathartic salts (magnesium oxide and magnesium sulphate). While stimulants and cathartic salts have been widely used, stimulants may cause intractable constipation via drug resistance if used consecutively for a long duration, and magnesium oxide may cause hypermagnesemia in elderly patients and patients with kidney malfunction.[9]

Recently, in addition to existing osmotic agents (macrogol 4000 often in combination with electrolytes, movicol, lactulose), new classes of laxatives have been developed for chronic constipation, including epithelial function transformation drugs (lubiprostone, linaclotide) and an ileal bile acid transporter (IBAT) inhibitor (elobixibat).

However, the evidence for the effectiveness of laxatives either conventional or recently developed for the treatment of chronic constipation in PD patients is not extensive, except for macrogol and lubiprostone, a chloride channel-2 activator, which have been shown to be significantly efficacious over placebo in improving bowel movement frequency.[10, 11] Although probiotics and prebiotic fibre were also proposed to be useful for the treatment of PD-related constipation,[12, 13] more evidence for different classes of laxatives is needed to expand therapeutic options for chronic constipation in PD patients.

Elobixibat is an inhibitor of IBAT, which is expressed in the distal ileum. Bile acids escape the reabsorption process via the action of this drug and then enter the large intestinal lumen.[14] The increased levels of bile acids may interact with transmembrane G-protein-coupled receptor (TGR5) molecules, leading to an influx of water and electrolytes into the lumen. The bile acid-TGR5 interaction also triggers serotonin release into the intestinal wall, which activates intrinsic primary afferent

neurons. This leads to an interneuron-mediated activation of motor neurons that finally activates large-intestinal motility,[15] inducing colonic high-amplitude propagated contractions.[16] Recently, a large-scale, multicenter, randomized, double-blind phase 3 study was conducted, revealing that elobixibat resolved idiopathic chronic constipation with no serious safety concerns.[17] Elobixibat is thus expected to be a novel option for the treatment of chronic constipation on the basis of its mode of action being totally different from those of the other existing laxatives.[18, 19]

We are planning to conduct a study to examine the efficacy and safety of elobixibat in PD patients with chronic constipation. The superiority of elobixibat over placebo will be explored in a randomized, double-blind, comparative study during 4-week daily administration of the drug to eligible patients. The drug will also be evaluated for its safety and potential impact on the underlying PD condition. The study methodology is detailed in this article.

METHODS AND ANALYSIS

The objective of this study is to explore a novel therapeutic option for chronic constipation in PD patients. The conduct of the present study was approved by the Juntendo University Certified Review Board.

Primary endpoints

The weekly frequency of spontaneous bowel movements with no assistance from rescue therapies such as bisacodyl suppositories, enema, disimpaction, etc. (see below) will be recorded during each 7-day segment of the treatment period (Week 0-1 up to Week 3-4; see Figure 1). Bowel movements observed within 24 hours of suppository use will not be counted. Changes in the frequency at Visit 4 (Week 4) from baseline (Visit 2/Week 0; see Figure 1) will be compared between the elobixibat group and the placebo group.

Secondary endpoints

Weekly changes from baseline in the frequency of spontaneous bowel movements and complete spontaneous bowel movements (i.e., no sensation of incomplete evacuation) will be assessed throughout the treatment period (Visit 4/Week 4; Figure 1). Changes from baseline in stool form will also be assessed up to Week 4 using the Bristol Scale.[20]

Use of rescue medication and questionnaire surveys using the Japanese version of Patient Assessment of Constipation Quality of Life (JPAC-QOL),[21] Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS),[22]

Parkinson's Disease Questionnaire-39 (PDQ-39),[23] and Euro-Qol 5 dimension – 5 level (EQ-5D-5L)[24,25] will be assessed. The use of dopamine preparations will also be monitored, since the effectiveness of elobixibat in improving constipation via increased levels of intestinal bile acids may also improve small intestinal absorption of the anti-Parkinsonian medications.

Subgroup analyses will be further performed for these endpoints by the presence or absence of complications, age (≥ or <65 years), Hoehn and Yahr scale (1 to 4), duration of the underlying disease (PD; ≥ or <median), dose equivalence of L-Dopa prior to elobixibat initiation, and duration of chronic constipation (≥ or <20 years).

Overall study design

This study is designed as a multicentre, randomised, double-blind, placebo-controlled, parallel-group study at 3 academic centres (Juntendo University Hospital, Juntendo University Urayasu Hospital, and Juntendo University Nerima Hospital), in which PD patients with chronic constipation will pre-prandially receive elobixibat (Goofice®; EA Pharma Co., Ltd., Tokyo, Japan) or its indistinguishable matched placebo once daily for four weeks, and the frequency of spontaneous bowel movements will be compared between the patients receiving either elobixibat or placebo. Safety information,

including adverse events (AEs) and discontinuation and interruption of the investigational drugs, will also be collected.

The study will consist of two periods, the observation period and the treatment period. It will be conducted from October 26, 2020 (date of the first announcement in the Japan Registry of Clinical Trials; jRCT) through September 30, 2022. As seen in Figure 1, we plan two steps for patient registration, temporary and final. At Week -2 (Visit 1) of the observation period, PD patients will be provided with the detailed information about the study. After providing written, informed consent for study participation, they will be temporarily registered based on the patient definitions (see below). Following the observation period, the patients will be further assessed for study participation at Week 0 (Visit 2). Once none of the exclusion criteria are confirmed to be applicable, the patients will be finally registered and assigned to either the elobixibat group or the placebo group in a double-blind manner (Figure 1). The eligible patients will visit their clinical sites twice more (Visit 3 at Week 2 and Visit 4 at Week 4) during the 4-week treatment period.

A Bowel Movement Diary will be provided at Week -2 (Visit 1, see below) to each patient, once temporarily registered. The patient will record drug use, bowel movements, etc. in the Diary daily throughout the study period.

Patient definitions

Patients will be diagnosed as having PD in reference to the diagnostic criteria defined by the International Parkinson and Movement Disorder Society (MDS)[26] and must be in stages 1 to 4 on the Hoehn and Yahr scale.[27] The diagnosis of chronic constipation will be made referring to the Rome IV-defined criteria.[28,29] Outpatients aged ≥20 years at the time of informed consent must have two or more of the following symptoms related to spontaneous bowel movements from at least 6 months before consent: i) <3 spontaneous bowel movements per week; ii) straining frequency >25% of defecations; iii) frequency of lumpy or hard stools >25% of defecations; and iv) sensation of incomplete evacuation >25% of defecations. Patients who meet these criteria will be temporarily registered, once written, informed consent is provided (Figure 1).

A PD patient will be excluded at temporary registration if he/she: has (or is suspected to have) organic constipation or dyschezia; is unable to use a rescue medication (bisacodyl 10 mg suppositories; Teleminsoft Suppositories® 10 mg, Cox Japan, Tokyo, Japan); currently has serious kidney dysfunction (creatinine ≥2.00 mg/dL), serious hepatic dysfunction (total bilirubin ≥3.0 mg/dL, or AST or ALT ≥100 U/L), or serious cardiac

dysfunction; has malignant tumour(s); has a history of hypersensitivity to elobixibat; is taking bile acid preparations (ursodeoxycholic acid, chenodeoxycholic acid), aluminium-containing preparations (sucralfate hydrate, aldioxa, etc.), cholestyramine, colestimide, digoxin, dabigatran etexilate mesylate, or midazolam; has a Mini–Mental State Examination (MMSE) score[30] ≤26; or is considered ineligible by the investigator or sub-investigator, hereinafter termed (sub)investigator, for study participation because of safety concerns, poor protocol compliance, etc. Female patients will also be excluded if they are pregnant, breastfeeding, or expecting pregnancy during the study period.

Patient exclusion is further scheduled at the final registration if one of the following cases applies to a patient during the 2-week observation period: use of the rescue medication (bisacodyl 10 mg suppositories) ≥5 times; use of the rescue medication within 72 hours post-bowel movement; experience of spontaneous bowel movement with mushy or watery stool according to Bristol Stool Form Scale type 6 or 7;[20] or use of prohibited medications/therapies (see below).

Study procedures and schedule

Registration of study patients and their allocation to the investigational drug will be

performed via an internet-mediated Interactive Web Response System (IWRS). The (sub)investigator (or study-assigned coordinator) will access the specific website for patient registration and allocation using a specific ID and password, and complete the necessary information about each anonymized patient. Investigational drug allocation will be instantly presented for each patient following eligibility judgment (see below). The schedule of this study is shown in Figure 2.

The (sub)investigator will give detailed explanations of this study to each PD patient who meets the inclusion criteria but not the exclusion criteria at Visit 1 and then obtain the patient's written, informed consent on a free will basis. The patient will be informed that he/she may withdraw his/her consent for any reason and at any time during the study period. The (sub)investigator will give the eligible patient a temporary identification code and enter the patient's background in the Eligibility for Temporary Registration form of the electronic Case Report Form (eCRF; see Figures 1 and 2).

The Bowel Movement Diary and rescue medication (bisacodyl 10 mg suppositories) will be provided to each patient at temporary registration. The (sub)investigator will instruct each patient how to complete the required items in the Diary.

At Visit 2, the (sub)investigator will judge the eligibility of each patient for final registration referring to the exclusion criteria (see above) and enter the background of

qualified patients in the Eligibility for Final Registration form of the eCRF. Once the patient's eligibility is confirmed, a final identification code will be assigned to the patient, who will be then allocated randomly to treatment group.

Drug allocation will be based on a stratified, permuted block method with sex as an allocation factor. Satt Co., Ltd. (Tokyo) will perform the allocation by preparing a drug allocation table using IWRS. The study drugs will be sealed with specific drug numbers and delivered to the individual institutional sites according to the allocation table. At the final registration of patients, the (sub)investigator will check the final identification code and the specific number of randomly allocated investigational drug for each qualified patient on the IWRS screen. The specifically numbered drug will be provided to the patient by the (sub)investigator at Visit 2 and Visit 3 for 2 weeks each time (3 tablets x 14 days), as described below. The key code of the allocation table will be opened by Satt after all study data has been locked.

The patient will start the 4-week treatment period with once-daily, preprandial intake of 2 tablets of investigational drug (elobixibat 10 mg) or its placebo. One tablet may be added on the next day if no spontaneous bowel movement is observed during the next 24 hours. If excessive effectiveness or discomfort appears, the dosage may be decreased at the direction of the (sub)investigator or the patient's judgment. Dose augmentation

from 1 tablet to 3 tablets will not be allowed. Interruption of the investigational drug due to the occurrence of an AE may be allowed at the direction of the (sub)investigator or the patient's judgment, but as-needed intake of the drug based on bowel movement status will not be acceptable. The drug may be restarted at the dose taken immediately before interruption or at a lower dose. Inappropriately long (≥7 consecutive days) or frequent (≥3 days per week during 2 consecutive weeks) interruption of the drug may lead to discontinuation of the patient from the study at the (sub)investigator's discretion.

Rescue and concomitant medications/therapies

Since this study is primarily planned to explore the efficacy and safety of elobixibat as a laxative in PD patients, concomitant medications will be used throughout the study period for parkinsonism except for Duodopa® pump therapy (Abbvie Inc., North Chicago, IL, USA) with levodopa/carbidopa hydrate intestinal gel. Bisacodyl 10 mg suppositories may be used once to twice daily as a rescue medication when no bowel movement is observed for 72 or more consecutive hours, unless emergency use is required.

Because of potential effects on the study results and/or interpretation thereof, use of the following drugs or therapies as concomitant medications will be prohibited throughout

the entire study period: laxatives other than elobixibat such as magnesium hydroxide, sodium picosulphate, sennosides, lubiprostone, linaclotide, polyethylene glycol (macrogol 4000), etc.; oriental medicines for constipation (daiokanzoto extract, choijokito extract, daisaikoto extract, etc.); medicines indicated for irritable bowel syndrome (IBS; ramosetron hydrochloride, polycarbophil calcium, trimebutine maleate, etc.); supplements or over-the-counter drugs to improve the constipated condition; enema or intestinal lavage; lavage solution for colonoscopy; drugs listed in the Precaution section of the package insert of elobixibat (Goofice® 5 mg tablets) as "with caution for concomitant use" (bile acid preparations such as ursodeoxycholic acid and chenodeoxycholic acid, aluminium-containing antacids such as sucralfate hydrate, aldioxa, etc., cholestyramine, cholestimid, digoxin, dabigatran etexylate methanesulfonate, and midazolam; other medicines or investigational drugs being used in clinical trials; non-internal therapy for constipation such as biofeedback therapy; disimpaction; and Duodopa® pump therapy. The patient should self-report in his/her Bowel Movement Diary when any of the drugs/agents/therapies listed above are used.

Discontinuation of the study

Participation of a recruited patient will be discontinued if any of the following

conditions is met: judged difficult to continue due to the onset of an AE; ineligibility confirmed after study initiation; lost to follow-up; confirmed or suspected pregnancy; voluntary withdrawal; repeated protocol violations; or any other reason for which the (sub)investigator judges that discontinuation would be necessary.

All study procedures will be discontinued if any of the following conditions is met: the Institutional Review Board of Juntendo University Hospital determines that the study should be discontinued; the appearance of safety concerns with potential impact on study progress; appearance of incidents or information that may potentially lead to impairment of ethical or scientific validity of the study; or appearance of any other incidents or information that may potentially lead to impairment of appropriateness of study conduct and/or reliability of study results.

Observations and measurements

Patient background, medical history and complications, and data of physical examinations will be collected at Visit 1 (Figure 2). On final judgment regarding study registration at Visit 2, subjective symptoms and objective findings, medical history and complications, physical examinations, and vital signs will be recorded for the eligible patients. Subjective symptoms and objective findings will be collected twice more at

Visits 3 and 4. Physical examinations and vital signs will also be recorded at Visit 4. The JPAC-QOL,[21] MDS-UPDRS,[22] PDQ-39,[23] and EQ-5D-5L,[24,25] surveys and laboratory measurements (haematology and blood chemistry) will be recorded at Visits 2 and 4 (Figure 2).

Each patient will receive a Bowel Movement Diary at Visit 1 and will then record daily the status of bowel movements (date, stool hardness based on the Bristol scale,[20] and sensation of incomplete evacuation), use of rescue medication (date, dose of bisacodyl suppositories) and concomitant medication (drugs for treatment of PD-related motor symptoms; date, drug name, dose), and treatment with non-investigational drugs and/or therapy for constipation. If the patient enters the treatment period, he/she will continue to record those items and also record daily use of the investigational drug (elobixibat or placebo; date and dose, i.e. number of tablets taken) in the Diary starting at Visit 2 up to the end of study (Visit 4). Discontinuation, if it occurs, should also be recorded in the Diary with its date and reason.

Safety information

This study will specifically focus on AEs that are suspected to have occurred in association with study conduct and include any of study conduct-associated events,

impairments, deaths, infections, laboratory abnormalities, and symptoms.

The (sub)investigator will examine the patient for AEs throughout the study period (Figure 2) and upon finding an event, record in the patient's eCRF its: name; onset date; severity (mild, moderate, or severe); seriousness (non-serious or serious); defined category of seriousness (death, life-threatening, hospitalization-initial or prolonged, disability or permanent damage, an event potentially leading to disability or permanent damage, ill condition judged as serious in reference to the aforementioned categories, or congenital anomaly or birth defect); predictability (known or unknown); action taken regarding the investigational drug (continuation, interruption, or discontinuation); outcome (recovered, improving, not recovered, recovered with sequelae, died, or unknown); date of outcome; causal relationship with use of the investigational drug ('not related' or grades other than 'not related'; suspected factor(s) other than the investigational drug should be recorded if judged 'not related').

Study population and statistical analysis

Based on the efficacy assessment of elobixibat vs. placebo in phase 2 and phase 3 clinical trials conducted in Japanese patients with chronic constipation,[17,31,32] the expected effect size was calculated as 3.06 (5.66 for elobixibat 10 mg vs. 2.60 for

placebo) with a common standard deviation of 4.15. Accordingly, we estimated a sample size of 40 patients for each group for 90% detection power at a two-sided significance level of 5%. Assuming a dropout rate of 20%, we plan to recruit 100 PD patients with chronic constipation in this study.

The full analysis set (FAS) is defined as the randomised population receiving at least one dose of the investigational drug with any measurement with regard to efficacy assessment. To ensure the robustness of study results, we also define a per-protocol set (PPS) as the population after the patients are excluded from the FAS due to any of the following reasons: any of the inclusion criteria inapplicable or any of the exclusion criteria applicable; a patient receiving the investigational drug with a non-allocated drug number; a patient receiving prohibited concomitant medications or therapies; a patient deemed to be inappropriate for study participation due to low drug compliance, lost to follow-up, lack of measurements, etc. The safety analysis set is defined as a population receiving at least one dose of the investigational drug after randomization.

Continuous variables and categorical variables will be presented as mean±standard deviation (SD) and as frequencies and percentages, respectively. Summary statistics may include medians and quartiles, as appropriate. Comparisons will be made for primary outcomes between the elobixibat group and the placebo group by analysis of

covariance (ANCOVA) using baseline values and sex as covariates. Adjusted means with 95% confidence intervals and p values will be presented at a two-sided significance level of 5%. Within-group variations will be assessed by paired *t*-tests. Missing values will be imputed by the last observation carried forward (LOCF) method. Safety data will be shown as frequencies and percentages by group and individual event.

PATIENT AND PUBLIC INVOLVEMENT

No formal patient advisory committee was established, and there was no patient or public involvement in the design and planning of the study.

ETHICS AND DISSEMINATION

This study will be conducted according to the protocol that has been prepared in accordance with the Helsinki Declaration, Clinical Trials Act of the Japan Ministry of Health, Labour and Welfare, and related laws and regulations. Each study patient will be anonymously identified by a specific identification code and hence protected against privacy invasion. The information and data of each patient will be used exclusively for the study purpose and will never be disseminated outside the study.

As a coordinating centre, SRD Co., Ltd. will share necessary information related to this

study at the participating medical organizations in this study, conduct operations aimed at facilitating this study, and provide support to investigators. Data management and monitoring are conducted by Juntendo Clinical Research and Trial Center, Juntendo University Hospital. Details are specified in the Data Management Plan and Monitoring Plan.

If a serious health hazard arises due to participation in this study, coverage benefits can be received from insurance carried by a principal investigator, provided, however, that compensation may be reduced or not compensated if it is proven that the health hazard was caused by the research subject's own wilful act or gross negligence. In addition, if there is no causal relationship between the newly occurring health hazard and the deterioration of the originally affected disease, it is not covered by compensation. After completion of the study by each research subject, the investigators will make efforts to provide the best medical care obtained from the results of the research.

The results obtained from this study will be disseminated through an online study registry, the Japan Registry of Clinical Trials (jRCT). The results will also be presented at relevant scientific conferences, such as a professional congress for movement disorders and Parkinson's disease, and in a relevant medical journal.

DISCUSSION AND DISSEMINATION

PD treatment is usually focused on the amelioration of movement dysfunction. However, patients with PD have many non-motor symptoms, especially autonomic dysfunction. Chronic constipation has been considered one of the troublesome symptoms affecting the QOL of PD patients, and it may even be life-threatening. Although fermented milk products containing probiotics and prebiotic fibres may have a favourable effect on PD-related constipation, they will not be available as laxatives. Although multiple classes of laxatives are available, there is little evidence supporting their use for PD-related constipation. An evidence-based medicine review[1] recommends only three drugs/foods for PD-related constipation, including macrogol, lubiprostone, and probiotics/prebiotic fibres. Two laxatives are considered "likely efficacious" and "possibly useful" for the treatment of constipation in PD patients based on the quality of randomised, controlled trials.

As mentioned above, gastrointestinal dysfunction is known to have one of the highest prevalences among the non-motor symptoms of PD. In addition, chronic constipation is known to be the earliest symptom of the prodromal phase of PD.[33] Furthermore, IBS is known to be one of the prodromal gastrointestinal symptoms[34] It has been reported that chronic constipation in PD might be caused by multiple mechanisms, including

decreased colonic motility, reflex inability of the pelvic floor muscles during attempted defecation, and IBS.[2,6] However, the precise mechanisms underlying constipation remain unknown. Thus, the same treatment algorithm used in patients with idiopathic chronic constipation should be recommended for constipation occurring in the patients with PD.[2] Elobixibat is a highly potent selective IBAT inhibitor that results in excess bile acids in the colon, which is associated with increased water influx from the colon and colon motility via an interaction with TGR5.[15] These action mechanisms produce favourable effects on idiopathic chronic constipation and IBS.[17] Considering the effectiveness of macrogol and lubiprostone against PD-accompanying constipation, elobixibat is also expected to improve this condition. This study will provide the first evidence of whether elobixibat is a useful treatment for chronic constipation in patients with PD, as has already been demonstrated for idiopathic chronic constipation.

We believe the randomised, clinical study proposed here will be useful for expanding treatment options for PD-related constipation in an evidence-based manner.

The study findings will be presented at relevant conferences and published in a peer-reviewed journal.

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Authors' Contributions

TH, GO, and NH were involved in conception and trial design. TH was involved in drafting of the article. TH, GO, YS, KO, NN, JF, RN, NK, TT, YO, SS, KN, HE, AF, AN, MK, DT, TO, HTA, HK, SN, and NH were involved in critical revision of the article for important intellectual content. All the authors were involved in final approval of the article. NY provided statistical expertise.

Data availability statement

Data are available on reasonable request (TH; thatano@juntendo.ac.jp).

Funding

This study will be funded by EA Pharma Co., Ltd. (Tokyo) and Mochida Pharmaceutical Co., Ltd. (Tokyo) (grant number: N/A). The two companies also provide clinical supplies, the Bowel Movement Diary, and other products necessary for

study conduct. It should be noted that the two companies and their employees will never be involved in any study procedures including collection, analysis or interpretation of data, ensuring (sub)investigators will be completely independent of the funders throughout study conduct.

Competing interests

There are no competing interests.

FIGURE LEGENDS

Figure 1 Study outline

Washout: previous medications except for anti-Parkinsonian medications will be washed out during the observation period.

Consent: written, informed consent

Exam.: physical examinations

Test: laboratory tests

Eligibility: eligibility confirmed for study participation

Alloc.: patient allocation to either treatment with elobixibat or with placebo

Prescrip.: prescription of the investigational medication according to patient allocation

Drug retrieval: unused/remaining investigational medications will be retrieved.

Figure 2 Study schedule

[a]: Allowance denotes the time window allowed relative to the date of Visit 1 for Visit 2 and Visit 2 for Visits 3 and 4.

[b]: Temporary registration for study participation

[c]: Final registration for study participation

Figure 1

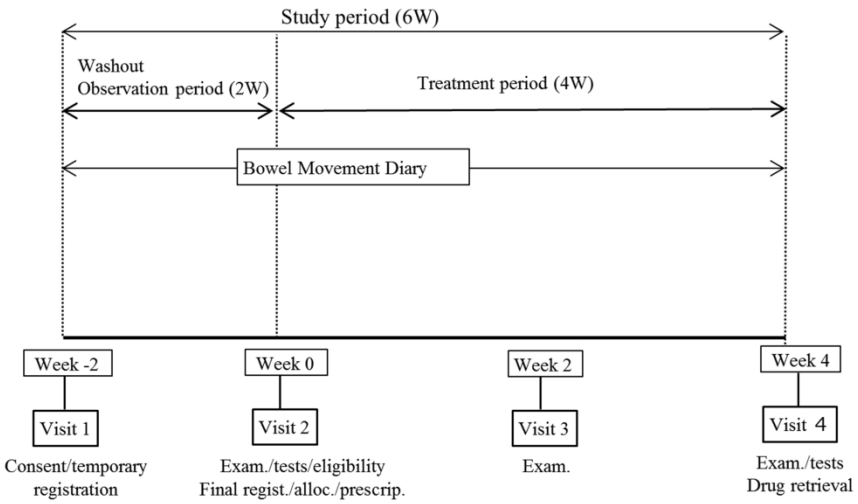

Figure 1 Study outline

254x190mm (307 x 307 DPI)

Figure 2

		Observation period	Administration start	Treatment period	
Visit		Visit 1	Visit 2	Visit 3	Visit 4
Date (Allowance[a])		14 days prior to Visit 2	Day 1 (≤ 5 days post-Visit 2)	Day 15 post Visit 2 (≤± 7 days))	Day 29 post Visit 2 (≤ 7 days) or discontinuation
Informed consent		○			
Eligibility confirmation		○ (Temp. regist.[b])	○ (Final regist.[c])		
Physical examinations	Patient background	○			
	Subjective symptoms/objective findings		○	○	○
	History/complications	○	○		
	Physical examinations	○	○		○
	Vital signs (blood pressure/pulse rate)		○		○
Bowel Movement Diary	Use of investigational medication		◄———	———	———►
	Use of rescue/concomitant medication	◄———	———	———	———►
	Bowel movement	◄———	———	———	———►
	Other therapy for constipation	◄———	———	———	———►
Adverse events		◄———	———	———	———►
JPAC-QOL			○		○
MDS-UPDRS			○		○
PDQ-39			○		○
EQ-5D			○		○
Laboratory tests	Haematology		○		○
	Blood chemistry		○		○

Figure 2 Study schedule

254x190mm (307 x 307 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	34
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 34
	5b	Name and contact information for the trial sponsor	34
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6-8
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	22, 23

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-8
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	6-8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-8, 10, 11
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11, 13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10, 11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15-17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13-15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-17
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	17, 18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig. 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19-21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	19-21
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13-15
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13-15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13-15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13-15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	19-21
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	19-21

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____22_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__8, 9, 10, 19-22___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___8, 9, 10_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__19-22_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____23_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____17,18_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___10-13_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____34, 35___
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____22, 23____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____10-13_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____14____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____NA____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__17, 21, 22___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__34, 35_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__34_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___22_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___26_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____34_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol: A multicentre, placebo-controlled, randomised, double-blind, parallel-group study investigating the efficacy and safety of elobixibat, an ileal bile acid transporter inhibitor, in patients with Parkinson's disease with chronic constipation (CONST-PD)

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Secondary Subject Heading:	Gastroenterology and hepatology
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Protocol: A multicentre, placebo-controlled, randomised, double-blind, parallel-group study investigating the efficacy and safety of elobixibat, an ileal bile acid transporter inhibitor, in patients with Parkinson's disease with chronic constipation (CONST-PD)

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ABSTRACT

Introduction

Chronic constipation worsens the quality of life (QOL) of Parkinson's disease (PD) patients. Elobixibat, an ileal bile acid transporter inhibitor, is a useful laxative, but its effect on chronic constipation in PD patients remains unclear. Therefore, we designed a placebo-controlled, randomised, double-blind study to investigate the efficacy and safety of elobixibat in PD patients with chronic constipation.

Methods and analysis

The study will consist of 2-week observation and 4-week treatment periods. Patients with clinically established PD will record the status of spontaneous bowel movements and use of rescue medications/concomitant medications in a Bowel Movement Diary from the start of the observation period at Visit 1 (Week -2). At Visit 2 (Week 0), patients will be assessed for final registration based on the Diary records and physical examinations, and allocated to either the elobixibat or placebo group. Daily intake of the investigational drug will be recorded in the Diary. Patients will undergo laboratory tests and answer constipation-related, PD-related, and QOL-related questionnaires at Visits 2 and 4 (Week 4). Subjective symptoms and objective findings will be collected at Visits 2, 3 (Week 2), and 4. Since patients' motor function might be improved by treatment of constipation, the use of dopamine preparations will also be monitored. Bowel movement data and other parameters will be compared between groups.

Safety information will be collected as adverse events, specifically focusing on those occurring in association with study conduct.

Ethics and dissemination

This study will be conducted in accordance with the Helsinki Declaration, the Clinical Trials Act of the Japan Ministry of Health, Labour and Welfare, and related laws and regulations. The study was approved by the Juntendo University Certified Review Board. The results will be disseminated through an online study registry (Japan Registry of Clinical Trials), presented at scientific conferences, and published in medical journals.

Registration number of this study: JPRN-jRCTs031200172 (Japan Primary Registries Network)

Keywords

Parkinson's disease, Motility disorders, Clinical trials

Strengths and limitations of the study

- The key strength of this study is its design as a randomized, double-blind, placebo-controlled trial to determine the efficacy and safety of elobixibat for Parkinson's disease patients with chronic constipation.
- A further strength is that it will examine not only the efficacy of elobixibat for PD-related constipation, but also its effects on quality of life and movement in PD patients.
- Because of the short study period (4-week administration), the long-term efficacy and safety of elobixibat may not be clarified.
- Bowel Movement Diary data might have limited credibility because they are based on the patients' subjective responses.

INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative disorders. Whereas PD is commonly considered a movement disorder, patients with PD have many difficulties with non-motor symptoms, such as dementia, anxiety, sleep disturbance, and autonomic dysfunction.[1] Chronic constipation is one of the common digestive complications experienced by PD patients even before or at an early stage of disease progression, with its frequency varying from 7% to 70% depending on the definition.[2-6] Since long-lasting constipation may decrease quality of life (QOL) and be occasionally accompanied by life-threatening intestinal perforation and/or megacolon syndrome, it should be appropriately controlled.[7,8]

Multiple types of laxatives are conventionally available for the treatment of chronic constipation, including bulk-forming agents such as carmellose sodium and dioctyl sodium sulfosuccinate, stimulants such as sennoside and sodium picosulphate hydrate, and osmotic agents such as cathartic salts (magnesium oxide and magnesium sulphate). While stimulants and cathartic salts have been widely used, stimulants may cause intractable constipation via drug resistance if used consecutively for a long duration, and magnesium oxide may cause hypermagnesemia in elderly patients and patients with kidney malfunction.[9]

Recently, in addition to existing osmotic agents (macrogol 4000 often in combination with electrolytes, movicol, lactulose), new classes of laxatives have been developed for chronic constipation, including epithelial function transformation drugs (lubiprostone, linaclotide) and an ileal bile acid transporter (IBAT) inhibitor (elobixibat).

However, the evidence for the effectiveness of laxatives either conventional or recently developed for the treatment of chronic constipation in PD patients is not extensive, except for macrogol and lubiprostone, a chloride channel-2 activator, which have been shown to be significantly efficacious over placebo in improving bowel movement frequency.[10, 11] Although probiotics and prebiotic fibre were also proposed to be useful for the treatment of PD-related constipation,[12, 13] more evidence for different classes of laxatives is needed to expand therapeutic options for chronic constipation in PD patients.

Elobixibat is an inhibitor of IBAT, which is expressed in the distal ileum. Bile acids escape the reabsorption process via the action of this drug and then enter the large intestinal lumen.[14] The increased levels of bile acids may interact with transmembrane G-protein-coupled receptor (TGR5) molecules, leading to an influx of water and electrolytes into the lumen. The bile acid-TGR5 interaction also triggers serotonin release into the intestinal wall, which activates intrinsic primary afferent

neurons. This leads to an interneuron-mediated activation of motor neurons that finally activates large-intestinal motility,[15] inducing colonic high-amplitude propagated contractions.[16] Recently, a large-scale, multicenter, randomized, double-blind phase 3 study was conducted, revealing that elobixibat resolved idiopathic chronic constipation with no serious safety concerns.[17] Elobixibat is thus expected to be a novel option for the treatment of chronic constipation on the basis of its mode of action being totally different from those of the other existing laxatives.[18, 19]

We are planning to conduct a study to examine the efficacy and safety of elobixibat in PD patients with chronic constipation. The superiority of elobixibat over placebo will be explored in a randomized, double-blind, comparative study during 4-week daily administration of the drug to eligible patients. The drug will also be evaluated for its safety and potential impact on the underlying PD condition. The study methodology is detailed in this article.

METHODS AND ANALYSIS

The objective of this study is to explore a novel therapeutic option for chronic constipation in PD patients. The conduct of the present study was approved by the Juntendo University Certified Review Board.

Primary endpoints

The weekly frequency of spontaneous bowel movements with no assistance from rescue therapies such as bisacodyl suppositories, enema, disimpaction, etc. (see below) will be recorded during each 7-day segment of the treatment period (Week 0-1 up to Week 3-4; see Figure 1). Bowel movements observed within 24 hours of suppository use will not be counted. Changes in the frequency at Visit 4 (Week 4) from baseline (Visit 2/Week 0; see Figure 1) will be compared between the elobixibat group and the placebo group.

Secondary endpoints

Weekly changes from baseline in the frequency of spontaneous bowel movements and complete spontaneous bowel movements (i.e., no sensation of incomplete evacuation) will be assessed throughout the treatment period (Visit 4/Week 4; Figure 1). Changes from baseline in stool form will also be assessed up to Week 4 using the Bristol Scale.[20]

Use of rescue medication and questionnaire surveys using the Japanese version of Patient Assessment of Constipation Quality of Life (JPAC-QOL),[21] Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS),[22]

Parkinson's Disease Questionnaire-39 (PDQ-39),[23] and Euro-Qol 5 dimension – 5 level (EQ-5D-5L)[24,25] will be assessed. The use of dopamine preparations will also be monitored, since the effectiveness of elobixibat in improving constipation via increased levels of intestinal bile acids may also improve small intestinal absorption of the anti-Parkinsonian medications.

Subgroup analyses will be further performed for these endpoints by the presence or absence of complications, age (≥ or <65 years), Hoehn and Yahr scale (1 to 4), duration of the underlying disease (PD; ≥ or <median), dose equivalence of L-Dopa prior to elobixibat initiation, and duration of chronic constipation (≥ or <20 years).

Overall study design

This study is designed as a multicentre, randomised, double-blind, placebo-controlled, parallel-group study at 3 academic centres (Juntendo University Hospital, Juntendo University Urayasu Hospital, and Juntendo University Nerima Hospital), in which PD patients with chronic constipation will pre-prandially receive elobixibat (Goofice®; EA Pharma Co., Ltd., Tokyo, Japan) or its indistinguishable matched placebo once daily for four weeks, and the frequency of spontaneous bowel movements will be compared between the patients receiving either elobixibat or placebo. Safety information,

including adverse events (AEs) and discontinuation and interruption of the investigational drugs, will also be collected.

The study will consist of two periods, the observation period and the treatment period. It will be conducted from October 26, 2020 (date of the first announcement in the Japan Registry of Clinical Trials; jRCT) through September 30, 2022. As seen in Figure 1, we plan two steps for patient registration, temporary and final. At Week -2 (Visit 1) of the observation period, PD patients will be provided with detailed information about the study. After providing written, informed consent for study participation, they will be temporarily registered based on the patient definitions (see below). Following the observation period, the patients will be further assessed for study participation at Week 0 (Visit 2). Once none of the exclusion criteria are confirmed to be applicable, the patients will be finally registered and assigned to either the elobixibat group or the placebo group in a double-blind manner (Figure 1). The eligible patients will visit their clinical sites twice more (Visit 3 at Week 2 and Visit 4 at Week 4) during the 4-week treatment period.

A Bowel Movement Diary will be provided at Week -2 (Visit 1, see below) to each patient, once temporarily registered. The patient will record drug use, bowel movements, etc. in the Diary daily throughout the study period.

Patient definitions

Patients will be diagnosed as having PD in reference to the diagnostic criteria defined by the International Parkinson and Movement Disorder Society (MDS)[26] and must be in stages 1 to 4 on the Hoehn and Yahr scale.[27] The diagnosis of chronic constipation will be made referring to the Rome IV-defined criteria.[28,29] Outpatients aged ≥20 years at the time of informed consent must have two or more of the following symptoms related to spontaneous bowel movements from at least 6 months before consent: i) <3 spontaneous bowel movements per week; ii) straining frequency >25% of defecations; iii) frequency of lumpy or hard stools >25% of defecations; and iv) sensation of incomplete evacuation >25% of defecations. Patients who meet these criteria will be temporarily registered, once written, informed consent is provided (Figure 1).

A PD patient will be excluded at temporary registration if he/she: has (or is suspected to have) organic constipation or dyschezia; is unable to use a rescue medication (bisacodyl 10 mg suppositories; Teleminsoft Suppositories® 10 mg, Cox Japan, Tokyo, Japan); currently has serious kidney dysfunction (creatinine ≥2.00 mg/dL), serious hepatic dysfunction (total bilirubin ≥3.0 mg/dL, or AST or ALT ≥100 U/L), or serious cardiac

dysfunction; has malignant tumour(s); has a history of hypersensitivity to elobixibat; is taking bile acid preparations (ursodeoxycholic acid, chenodeoxycholic acid), aluminium-containing preparations (sucralfate hydrate, aldioxa, etc.), cholestyramine, colestimide, digoxin, dabigatran etexilate mesylate, or midazolam; has a Mini–Mental State Examination (MMSE) score[30] ≤26; or is considered ineligible by the investigator or sub-investigator, hereinafter termed (sub)investigator, for study participation because of safety concerns, poor protocol compliance, etc. Female patients will also be excluded if they are pregnant, breastfeeding, or expecting pregnancy during the study period.

Patient exclusion is further scheduled at the final registration if one of the following cases applies to a patient during the 2-week observation period: use of the rescue medication (bisacodyl 10 mg suppositories) ≥5 times; use of the rescue medication within 72 hours post-bowel movement; experience of spontaneous bowel movement with mushy or watery stool according to Bristol Stool Form Scale type 6 or 7;[20] or use of prohibited medications/therapies (see below).

Study procedures and schedule

Registration of study patients and their allocation to the investigational drug will be

performed via an internet-mediated Interactive Web Response System (IWRS). The (sub)investigator (or study-assigned coordinator) will access the specific website for patient registration and allocation using a specific ID and password, and complete the necessary information about each anonymized patient. Investigational drug allocation will be instantly presented for each patient following eligibility judgment (see below). The schedule of this study is shown in Figure 2.

The (sub)investigator will give detailed explanations of this study to each PD patient who meets the inclusion criteria but not the exclusion criteria at Visit 1 and then obtain the patient's written, informed consent on a free will basis. The patient will be informed that he/she may withdraw his/her consent for any reason and at any time during the study period. The (sub)investigator will give the eligible patient a temporary identification code and enter the patient's background in the Eligibility for Temporary Registration form of the electronic Case Report Form (eCRF; see Figures 1 and 2).

The Bowel Movement Diary and rescue medication (bisacodyl 10 mg suppositories) will be provided to each patient at temporary registration. The (sub)investigator will instruct each patient how to complete the required items in the Diary.

At Visit 2, the (sub)investigator will judge the eligibility of each patient for final registration referring to the exclusion criteria (see above) and enter the background of

qualified patients in the Eligibility for Final Registration form of the eCRF. Once the patient's eligibility is confirmed, a final identification code will be assigned to the patient, who will be then allocated randomly to treatment group.

Drug allocation will be based on a stratified, permuted block method with sex as an allocation factor. Satt Co., Ltd. (Tokyo) will perform the allocation by preparing a drug allocation table using IWRS. The study drugs will be sealed with specific drug numbers and delivered to the individual institutional sites according to the allocation table. At the final registration of patients, the (sub)investigator will check the final identification code and the specific number of randomly allocated investigational drug for each qualified patient on the IWRS screen. The specifically numbered drug will be provided to the patient by the (sub)investigator at Visit 2 and Visit 3 for 2 weeks each time (3 tablets x 14 days), as described below. The key code of the allocation table will be opened by Satt after all study data have been locked.

The patient will start the 4-week treatment period with once-daily, preprandial intake of 2 tablets of investigational drug (elobixibat 10 mg) or its placebo. One tablet may be added on the next day if no spontaneous bowel movement is observed during the next 24 hours. If excessive effectiveness or discomfort appears, the dosage may be decreased at the direction of the (sub)investigator or the patient's judgment. Dose augmentation

from 1 tablet to 3 tablets will not be allowed. Interruption of the investigational drug due to the occurrence of an AE may be allowed at the direction of the (sub)investigator or the patient's judgment, but as-needed intake of the drug based on bowel movement status will not be acceptable. The drug may be restarted at the dose taken immediately before interruption or at a lower dose. Inappropriately long (≥7 consecutive days) or frequent (≥3 days per week during 2 consecutive weeks) interruption of the drug may lead to discontinuation of the patient from the study at the (sub)investigator's discretion.

Rescue and concomitant medications/therapies

Since this study is primarily planned to explore the efficacy and safety of elobixibat as a laxative in PD patients, concomitant medications will be used throughout the study period for parkinsonism except for Duodopa® pump therapy (Abbvie Inc., North Chicago, IL, USA) with levodopa/carbidopa hydrate intestinal gel. Bisacodyl 10 mg suppositories may be used once to twice daily as a rescue medication when no bowel movement is observed for 72 or more consecutive hours, unless emergency use is required.

Because of potential effects on the study results and/or interpretation thereof, use of the following drugs or therapies as concomitant medications will be prohibited throughout

the entire study period: laxatives other than elobixibat such as magnesium hydroxide, sodium picosulphate, sennosides, lubiprostone, linaclotide, polyethylene glycol (macrogol 4000), etc.; oriental medicines for constipation (daiokanzoto extract, choijokito extract, daisaikoto extract, etc.); medicines indicated for irritable bowel syndrome (IBS; ramosetron hydrochloride, polycarbophil calcium, trimebutine maleate, etc.); supplements or over-the-counter drugs to improve the constipated condition; enema or intestinal lavage; lavage solution for colonoscopy; drugs listed in the Precaution section of the package insert of elobixibat (Goofice® 5 mg tablets) as "with caution for concomitant use" (bile acid preparations such as ursodeoxycholic acid and chenodeoxycholic acid, aluminium-containing antacids such as sucralfate hydrate, aldioxa, etc., cholestyramine, cholestimid, digoxin, dabigatran etexylate methanesulfonate, and midazolam; other medicines or investigational drugs being used in clinical trials; non-internal therapy for constipation such as biofeedback therapy; disimpaction; and Duodopa® pump therapy. The patient should self-report in his/her Bowel Movement Diary when any of the drugs/agents/therapies listed above are used.

Discontinuation of the study

Participation of a recruited patient will be discontinued if any of the following

conditions is met: judged difficult to continue due to the onset of an AE; ineligibility confirmed after study initiation; lost to follow-up; confirmed or suspected pregnancy; voluntary withdrawal; repeated protocol violations; or any other reason for which the (sub)investigator judges that discontinuation would be necessary.

All study procedures will be discontinued if any of the following conditions is met: the Institutional Review Board of Juntendo University Hospital determines that the study should be discontinued; the appearance of safety concerns with potential impact on study progress; appearance of incidents or information that may potentially lead to impairment of ethical or scientific validity of the study; or appearance of any other incidents or information that may potentially lead to impairment of appropriateness of study conduct and/or reliability of study results.

Observations and measurements

Patient background, medical history and complications, and data of physical examinations will be collected at Visit 1 (Figure 2). On final judgment regarding study registration at Visit 2, subjective symptoms and objective findings, medical history and complications, physical examinations, and vital signs will be recorded for the eligible patients. Subjective symptoms and objective findings will be collected twice more at

Visits 3 and 4. Physical examinations and vital signs will also be recorded at Visit 4. The JPAC-QOL,[21] MDS-UPDRS,[22] PDQ-39,[23] and EQ-5D-5L[24,25] surveys and laboratory measurements (haematology and blood chemistry) will be recorded at Visits 2 and 4 (Figure 2).

Each patient will receive a Bowel Movement Diary at Visit 1 and will then record daily the status of bowel movements (date, stool hardness based on the Bristol scale,[20] and sensation of incomplete evacuation), use of rescue medication (date, dose of bisacodyl suppositories) and concomitant medication (drugs for treatment of PD-related motor symptoms; date, drug name, dose), and treatment with non-investigational drugs and/or therapy for constipation. If the patient enters the treatment period, he/she will continue to record those items and also record daily use of the investigational drug (elobixibat or placebo; date and dose, i.e. number of tablets taken) in the Diary starting at Visit 2 up to the end of study (Visit 4). Discontinuation, if it occurs, should also be recorded in the Diary with its date and reason.

Safety information

This study will specifically focus on AEs that are suspected to have occurred in association with study conduct and include any of study conduct-associated events,

impairments, deaths, infections, laboratory abnormalities, and symptoms.

The (sub)investigator will examine the patient for AEs throughout the study period (Figure 2) and upon finding an event, record in the patient's eCRF its: name; onset date; severity (mild, moderate, or severe); seriousness (non-serious or serious); defined category of seriousness (death, life-threatening, hospitalization-initial or prolonged, disability or permanent damage, an event potentially leading to disability or permanent damage, ill condition judged as serious in reference to the aforementioned categories, or congenital anomaly or birth defect); predictability (known or unknown); action taken regarding the investigational drug (continuation, interruption, or discontinuation); outcome (recovered, improving, not recovered, recovered with sequelae, died, or unknown); date of outcome; causal relationship with use of the investigational drug ('not related' or grades other than 'not related'; suspected factor(s) other than the investigational drug should be recorded if judged 'not related').

Study population and statistical analysis

Based on the efficacy assessment of elobixibat vs. placebo in phase 2 and phase 3 clinical trials conducted in Japanese patients with chronic constipation,[17,31,32] the expected effect size was calculated as 3.06 (5.66 for elobixibat 10 mg vs. 2.60 for

placebo) with a common standard deviation of 4.15. Accordingly, we estimated a sample size of 40 patients for each group for 90% detection power at a two-sided significance level of 5%. Assuming a dropout rate of 20%, we plan to recruit 100 PD patients with chronic constipation in this study.

The full analysis set (FAS) is defined as the randomised population receiving at least one dose of the investigational drug with any measurement with regard to efficacy assessment. To ensure the robustness of study results, we also define a per-protocol set (PPS) as the population after the patients are excluded from the FAS due to any of the following reasons: any of the inclusion criteria inapplicable or any of the exclusion criteria applicable; a patient receiving the investigational drug with a non-allocated drug number; a patient receiving prohibited concomitant medications or therapies; a patient deemed to be inappropriate for study participation due to low drug compliance, lost to follow-up, lack of measurements, etc. The safety analysis set is defined as a population receiving at least one dose of the investigational drug after randomization.

Continuous variables and categorical variables will be presented as mean±standard deviation (SD) and as frequencies and percentages, respectively. Summary statistics may include medians and quartiles, as appropriate. Comparisons will be made for primary outcomes between the elobixibat group and the placebo group by analysis of

covariance (ANCOVA) using baseline values and sex as covariates. Adjusted means with 95% confidence intervals and p values will be presented at a two-sided significance level of 5%. Within-group variations will be assessed by paired *t*-tests. Missing values will be imputed by the last observation carried forward (LOCF) method. Safety data will be shown as frequencies and percentages by group and individual event.

PATIENT AND PUBLIC INVOLVEMENT

No formal patient advisory committee was established, and there was no patient or public involvement in the design and planning of the study.

ETHICS AND DISSEMINATION

This study will be conducted according to the protocol that has been prepared in accordance with the Helsinki Declaration, Clinical Trials Act of the Japan Ministry of Health, Labour and Welfare, and related laws and regulations. Each study patient will be anonymously identified by a specific identification code and hence protected against privacy invasion. The information and data of each patient will be used exclusively for the study purpose and will never be disseminated outside the study.

As a coordinating centre, SRD Co., Ltd. will share necessary information related to this

study at the participating medical organizations in this study, conduct operations aimed at facilitating this study, and provide support to investigators. Data management and monitoring are conducted by Juntendo Clinical Research and Trial Center, Juntendo University Hospital. Details are specified in the Data Management Plan and Monitoring Plan.

If a serious health hazard arises due to participation in this study, coverage benefits can be received from insurance carried by a principal investigator, provided, however, that compensation may be reduced or not compensated if it is proven that the health hazard was caused by the research subject's own wilful act or gross negligence. In addition, if there is no causal relationship between the newly occurring health hazard and the deterioration of the originally affected disease, it is not covered by compensation. After completion of the study by each research subject, the investigators will make efforts to provide the best medical care obtained from the results of the research.

The results obtained from this study will be disseminated through an online study registry (Japan Registry of Clinical Trials). The results will also be presented at relevant scientific conferences, such as a professional congress for movement disorders and Parkinson’s disease, and in relevant medical journals.

DISCUSSION AND DISSEMINATION

PD treatment is usually focused on the amelioration of movement dysfunction. However, patients with PD have many non-motor symptoms, especially autonomic dysfunction. Chronic constipation has been considered one of the troublesome symptoms affecting the QOL of PD patients, and it may even be life-threatening. Although fermented milk products containing probiotics and prebiotic fibres may have a favourable effect on PD-related constipation, they will not be available as laxatives. Although multiple classes of laxatives are available, there is little evidence supporting their use for PD-related constipation. An evidence-based medicine review[1] recommends only three drugs/foods for PD-related constipation, including macrogol, lubiprostone, and probiotics/prebiotic fibres. Two laxatives are considered "likely efficacious" and "possibly useful" for the treatment of constipation in PD patients based on the quality of randomised, controlled trials.

As mentioned above, gastrointestinal dysfunction is known to have one of the highest prevalences among the non-motor symptoms of PD. In addition, chronic constipation is known to be the earliest symptom of the prodromal phase of PD.[33] Furthermore, IBS is known to be one of the prodromal gastrointestinal symptoms.[34] It has been reported that chronic constipation in PD might be caused by multiple mechanisms, including

decreased colonic motility, reflex inability of the pelvic floor muscles during attempted defecation, and IBS.[2,6] However, the precise mechanisms underlying constipation remain unknown. Thus, the same treatment algorithm used in patients with idiopathic chronic constipation should be recommended for constipation occurring in patients with PD.[2] Elobixibat is a highly potent selective IBAT inhibitor that results in excess bile acids in the colon, which is associated with increased water influx from the colon and colon motility via an interaction with TGR5.[15] These action mechanisms produce favourable effects on idiopathic chronic constipation and IBS.[17] Considering the effectiveness of macrogol and lubiprostone against PD-accompanying constipation, elobixibat is also expected to improve this condition. This study will provide the first evidence of whether elobixibat is a useful treatment for chronic constipation in patients with PD, as has already been demonstrated for idiopathic chronic constipation.

We believe the randomised, clinical study proposed here will be useful for expanding treatment options for PD-related constipation in an evidence-based manner.

The study findings will be presented at relevant conferences and published in a peer-reviewed journal.

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Authors' Contributions

TH, GO, and NH were involved in conception and trial design. TH was involved in drafting of the article. TH, GO, YS, KO, NN, JF, RN, NK, TT, YO, SS, KN, HE, AF, AN, MK, DT, TO, HTA, HK, SN, and NH were involved in critical revision of the article for important intellectual content. All the authors were involved in final approval of the article. NY provided statistical expertise.

Data availability statement

Data are available on reasonable request (TH; thatano@juntendo.ac.jp).

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study conduct. It should be noted that the two companies and their employees will never be involved in any study procedures including collection, analysis or interpretation of data, ensuring (sub)investigators will be completely independent of the funders throughout study conduct.

Competing interests

There are no competing interests.

FIGURE LEGENDS

Figure 1 Study outline

Washout: previous medications except for anti-Parkinsonian medications will be washed out during the observation period.

Consent: written, informed consent

Exam.: physical examinations

Test: laboratory tests

Eligibility: eligibility confirmed for study participation

Alloc.: patient allocation to either treatment with elobixibat or with placebo

Prescrip.: prescription of the investigational medication according to patient allocation

Drug retrieval: unused/remaining investigational medications will be retrieved.

Figure 2 Study schedule

[a]: Allowance denotes the time window allowed relative to the date of Visit 1 for Visit 2 and Visit 2 for Visits 3 and 4.

[b]: Temporary registration for study participation

[c]: Final registration for study participation

Figure 1

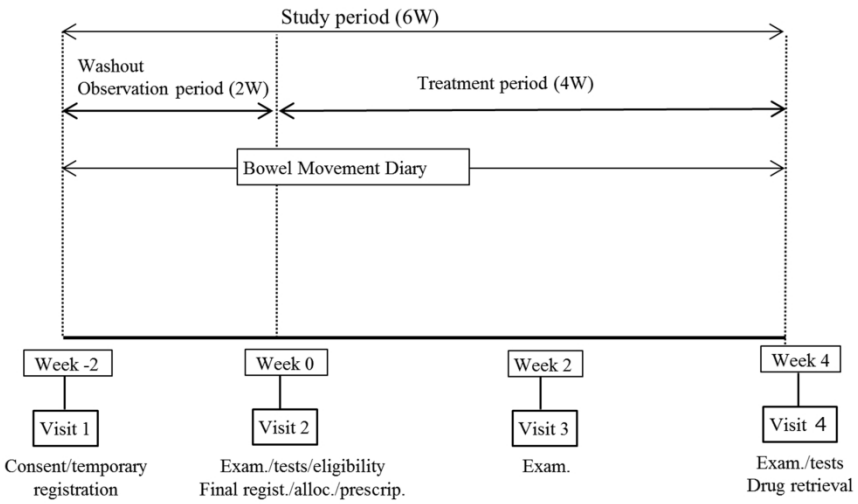

Figure 1 Study outline

254x190mm (307 x 307 DPI)

Figure 2

		Observation period	Administration start	Treatment period	
Visit		Visit 1	Visit 2	Visit 3	Visit 4
Date (Allowance[a])		14 days prior to Visit 2	Day 1 (≤ 5 days post-Visit 2)	Day 15 post Visit 2 (≤± 7 days))	Day 29 post Visit 2 (≤ 7 days) or discontinuation
Informed consent		○			
Eligibility confirmation		○ (Temp. regist.[b])	○ (Final regist.[c])		
Physical examinations	Patient background	○			
	Subjective symptoms/objective findings		○	○	○
	History/complications	○	○		
	Physical examinations	○	○		○
	Vital signs (blood pressure/pulse rate)		○		○
Bowel Movement Diary	Use of investigational medication		◄———	———	———►
	Use of rescue/concomitant medication	◄———	———	———	———►
	Bowel movement	◄———	———	———	———►
	Other therapy for constipation	◄———	———	———	———►
Adverse events		◄———	———	———	———►
JPAC-QOL			○		○
MDS-UPDRS			○		○
PDQ-39			○		○
EQ-5D			○		○
Laboratory tests	Haematology		○		○
	Blood chemistry		○		○

Figure 2 Study schedule

254x190mm (307 x 307 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	34
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 34
	5b	Name and contact information for the trial sponsor	34
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6-8
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	22, 23

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-8
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	6-8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-8, 10, 11
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11, 13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10, 11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15-17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13-15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-17
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	17, 18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig. 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19-21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	19-21
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13-15
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13-15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13-15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13-15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	19-21
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	19-21

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____22_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__8, 9, 10, 19-22___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___8, 9, 10_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__19-22_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____23_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	____17,18_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___10-13_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____34, 35___
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____22, 23____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____10-13_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____14____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____NA____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__17, 21, 22___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__34, 35_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__34_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___22_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___26_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____34_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.