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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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6 **A multicentre, placebo-controlled, randomised, double-blind, parallel-group study**
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9 **investigating the efficacy and safety of elobixibat, an ileal bile acid transporter**
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12 **inhibitor, in patients with Parkinson's disease with chronic constipation**
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15 **(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

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5 those occurring in association with study conduct.
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10 **Ethics and dissemination**

11
12 This study will be conducted in accordance with the Helsinki declaration, the Clinical
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14 Trials Act of the Japan Ministry of Health, Labour and Welfare, and related laws and
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16 regulations. All patient data will be anonymized to protect privacy and used only for the
17
18 study purpose.
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26 **Registration number of this study:** JPRN-jRCTs031200172 (Japan Primary Registries
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28 Network)
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38 **Keywords**

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40 Parkinson's disease, Motility disorders, Clinical trials
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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]

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

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

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41
42 Elobixibat is an inhibitor of IBAT, which is expressed in the distal ileum. Bile acids
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45 escape the reabsorption process via the action of this drug and then enter the large
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48 intestinal lumen.[14] The increased levels of bile acids may lead to an influx of water
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51 and electrolytes into the lumen, inducing colonic high-amplitude propagated
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54 contractions (HAPCs). Elobixibat is thus expected to be a novel option for the treatment
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57 of chronic constipation on the basis of its mode of action being totally different from
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6 those of the other existing laxatives.[15, 16]
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9 We are planning to conduct a study to examine the efficacy and safety of elobixibat in
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11 PD patients with chronic constipation. The superiority of elobixibat over placebo will be
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13 explored in a randomized, double-blind, comparative study during 4-week daily
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15 administration of the drug to eligible patients. The drug will also be evaluated for its
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17 safety and potential impact on the underlying PD condition. This study was approved by
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19 the Ethics Committee of the Juntendo University School of Medicine (J20-009). The
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21 study methodology is detailed in this article.
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32 **METHODS AND ANALYSIS**

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35 The objective of this study is to explore a novel therapeutic option for chronic
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37 constipation in PD patients.
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45 **Primary endpoints**

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47 The weekly frequency of spontaneous bowel movements with no assistance from rescue
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49 therapies such as bisacodyl suppositories, enema, disimpaction, etc. (see below) will be
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51 recorded during each 7-day segment of the treatment period (Week 0-1 up to Week 3-4;
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53 see Figure 1). Bowel movements observed within 24 hours of suppository use will not
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6 be counted. Changes in the frequency at Visit 4 (Week 4) from baseline (Visit 2/Week
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9 0; see Figure 1) will be compared between the elobixibat group and the placebo group.

15 **Secondary endpoints**

17
18 Weekly changes from baseline in the frequency of spontaneous bowel movements and
19
20 complete spontaneous bowel movements (i.e., no sensation of incomplete evacuation)
21
22 will be assessed throughout the treatment period (Visit 4/Week 4; Figure 1). Changes
23
24 from baseline in stool form will also be assessed up to Week 4 using the Bristol
25
26
27 Scale.[17]

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32 Use of rescue medication and questionnaire surveys using the Japanese version of
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34 Patient Assessment of Constipation Quality of Life (JPAC-QOL),[18] Movement
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36 Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS),[19]
37
38 Parkinson's Disease Questionnaire-39 (PDQ-39),[20] and Euro-Qol 5 dimension – 5
39
40 level (EQ-5D-5L)[21,22] will be assessed. The use of dopamine preparations will also
41
42 be monitored, since the effectiveness of elobixibat in improving constipation via
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44 increased levels of intestinal bile acids may also improve small intestinal absorption of
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46 the anti-Parkinsonian medications.

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

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6 and dose of investigational drug.
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11 **Overall study design**

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15 This study is designed as a randomised, double-blind, placebo-controlled, parallel-group
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18 study at 2 academic centres (Juntendo University Urayasu Hospital, and Juntendo
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21 University Nerima Hospital), in which PD patients with chronic constipation will
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24 pre-prandially receive elobixibat (Goofice®; EA Pharma Co., Ltd., Tokyo, Japan) or its
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26
27 indistinguishable matched placebo once daily for four weeks, and the frequency of
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29
30 spontaneous bowel movements will be compared between the patients receiving either
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32
33 elobixibat or placebo. Safety information, including adverse events (AEs) and
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35
36 discontinuation and interruption of the investigational drugs, will also be collected.
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38

39 The study will consist of two periods, the observation period and the treatment period. It
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41
42 will be conducted from October 26, 2020 (date of the first announcement in the Japan
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44
45 Registry of Clinical Trials; jRCT) through September 30, 2022. As seen in Figure 1, we
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47
48 plan two steps for patient registration, temporary and final. At Week -2 (Visit 1) of the
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51 observation period, PD patients will be provided with the detailed information about the
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54 study. After providing written, informed consent for study participation, they will be
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57 temporarily registered based on the patient definitions (see below). Following the
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6 observation period, the patients will be further assessed for study participation at Week
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9 0 (Visit 2). Once none of the exclusion criteria are confirmed to be applicable, the
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12 patients will be finally registered and assigned to either the elobixibat group or the
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14
15 placebo group in a double-blind manner (Figure 1). The eligible patients will visit their
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17
18 clinical sites twice more (Visit 3 at Week 2 and Visit 4 at Week 4) during the 4-week
19
20
21 treatment period.
22

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24 A Bowel Movement Diary will be provided at Week -2 (Visit 1, see below) to each
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27 patient, once temporarily registered. The patient will record drug use, bowel movements,
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29
30 etc. in the Diary daily throughout the study period.
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33 34 35 36 **Patient definitions**

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39 Patients will be diagnosed as having PD in reference to the diagnostic criteria defined
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41
42 by the International Parkinson and Movement Disorder Society (MDS)[23] and must be
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44
45 in stages 1 to 4 on the Hoehn and Yahr scale.[24] The diagnosis of chronic constipation
46
47
48 will be made referring to the Rome IV-defined criteria.[25,26] Outpatients aged ≥ 20
49
50
51 years at the time of informed consent must have two or more of the following symptoms
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53
54 related to spontaneous bowel movements from at least 6 months before consent: i) < 3
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57 spontaneous bowel movements per week; ii) straining frequency $> 25\%$ of defecations;
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6 iii) frequency of lumpy or hard stools >25% of defecations; and iv) sensation of
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9 incomplete evacuation >25% of defecations. Patients who meet these criteria will be
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11 temporarily registered, once written, informed consent is provided (Figure 1).
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18 A PD patient will be excluded at temporary registration if he/she: has (or is suspected to
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20 have) organic constipation or dyschezia; is unable to use a rescue medication (bisacodyl
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22 10 mg suppositories; Teleminsoft Suppositories® 10 mg, Cox Japan, Tokyo, Japan);
23
24 currently has serious kidney dysfunction (creatinine ≥ 2.00 mg/dL), serious hepatic
25
26 dysfunction (total bilirubin ≥ 3.0 mg/dL, or AST or ALT ≥ 100 U/L), or serious cardiac
27
28 dysfunction; has malignant tumour(s); has a history of hypersensitivity to elobixibat; is
29
30 taking bile acid preparations (ursodeoxycholic acid, chenodeoxycholic acid),
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32 aluminium-containing preparations (sucralfate hydrate, aldioxa, etc.), cholestyramine,
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34 colestimide, digoxin, dabigatran etexilate mesylate, or midazolam; has a Mini-Mental
35
36 State Examination (MMSE) score[27] ≤ 26 ; or is considered ineligible by the
37
38 investigator or sub-investigator, hereinafter termed (sub)investigator, for study
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40 participation because of safety concerns, poor protocol compliance, etc. Female patients
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42 will also be excluded if they are pregnant, breastfeeding, or expecting pregnancy during
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44 the study period.
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6 Patient exclusion is further scheduled at the final registration if one of the following
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9 cases applies to a patient during the 2-week observation period: use of the rescue
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11 medication (bisacodyl 10 mg suppositories) ≥ 5 times; use of the rescue medication
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13 within 72 hours post-bowel movement; experience of spontaneous bowel movement
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15 with mushy or watery stool according to Bristol Stool Form Scale (BSFS) type 6 or
16
17 7;^[17] or use of prohibited medications/therapies (see below).
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27 **Study procedures and schedule**

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30 Registration of study patients and their allocation to the investigational drug will be
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32 performed via an internet-mediated Interactive Web Response System (IWRS). The
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34 (sub)investigator (or study-assigned coordinator) will access the specific website for
35
36 patient registration and allocation using a specific ID and password and complete the
37
38 necessary information about each anonymized patient. Investigational drug allocation
39
40 will be instantly presented for each patient following eligibility judgment. Drug
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42 allocation will be based on a stratified, permuted block method with sex as an allocation
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44 factor.
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54 The schedule of this study is shown in Figure 2.

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57 The (sub)investigator will give detailed explanations of this study to each PD patient
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6 who meets the inclusion criteria but not the exclusion criteria at Visit 1 and then obtain
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8
9 the patient's written, informed consent on a free will basis. The patient will be informed
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12 that he/she may withdraw his/her consent for any reason and at any time during the
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15 study period. The (sub)investigator will give the eligible patient a temporary
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17
18 identification code and enter the patient's background in the Eligibility for Temporary
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21 Registration form of the electronic Case Report Form (eCRF; see Figures 1 and 2).
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24 The Bowel Movement Diary and rescue medication (bisacodyl 10 mg suppositories)
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26
27 will be provided to each patient at temporary registration. The (sub)investigator will
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29
30 instruct each patient how to complete the required items in the Diary.
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32
33 At Visit 2, the (sub)investigator will judge the eligibility of each patient for final
34
35
36 registration referring to the exclusion criteria (see above) and enter the background of
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38
39 qualified patients in the Eligibility for Final Registration form of the eCRF. Once the
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42 patient's eligibility is confirmed, a final identification code will be assigned to the
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45 patient, who will be then allocated randomly to treatment group. The (sub)investigator
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47
48 will check the final identification code and the allocated investigational drug number for
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50
51 each qualified patient on the IWRS screen. The specifically numbered drug will be
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54 provided to the patient by the (sub)investigator at Visit 2 and Visit 3 for 2 weeks each
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56
57 time (3 tablets x 14 days), as described below.
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6 The patient will start the 4-week treatment period with once-daily, preprandial intake of
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9 2 tablets of investigational drug (elobixibat 10 mg) or its placebo. One tablet may be
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12 added on the next day if no spontaneous bowel movement is observed during the next
13
14
15 24 hours. If excessive effectiveness or discomfort appears, the dosage may be decreased
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18 at the direction of the (sub)investigator or the patient's judgment. Dose augmentation
19
20
21 from 1 tablet to 3 tablets will not be allowed. Interruption of the investigational drug
22
23
24 due to the occurrence of an AE may be allowed at the direction of the (sub)investigator
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26
27 or the patient's judgment, but as-needed intake of the drug based on bowel movement
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30 status will not be acceptable. The drug may be restarted at the dose taken immediately
31
32
33 before interruption or at a lower dose. Inappropriately long (≥ 7 consecutive days) or
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36 frequent (≥ 3 days per week during 2 consecutive weeks) interruption of the drug may
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39 lead to discontinuation of the patient from the study at the (sub)investigator's discretion.
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45 **Rescue and concomitant medications/therapies**

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48 Since this study is primarily planned to explore the efficacy and safety of elobixibat as a
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51 laxative in PD patients, concomitant medications will be used throughout the study
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53
54 period for parkinsonism except for Duodopa[®] pump therapy (Abbvie Inc., North
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56
57 Chicago, IL, USA) with levodopa/carbidopa hydrate intestinal gel. Bisacodyl 10 mg
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6 suppositories may be used once to twice daily as a rescue medication when no bowel
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9 movement is observed for 72 or more consecutive hours, unless emergency use is
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12 required.

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15 Because of potential effects on the study results and/or interpretation thereof, use of the
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18 following drugs or therapies as concomitant medications will be prohibited: laxatives
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21 other than elobixibat such as magnesium hydroxide, sodium picosulphate, sennosides,
22
23
24 lubiprostone, linaclotide, polyethylene glycol (macrogol 4000), etc.; oriental medicines
25
26
27 for constipation (daiokanzoto extract, choijokito extract, daisaikoto extract, etc.);
28
29
30 medicines indicated for irritable bowel syndrome (ramosetron hydrochloride,
31
32
33 polycarbophil calcium, trimebutine maleate, etc.); supplements or over-the-counter
34
35
36 drugs to improve the constipated condition; enema or intestinal lavage; lavage solution
37
38
39 for colonoscopy; drugs listed in the Precaution section of the package insert of
40
41
42 elobixibat (Goofice® 5 mg tablets) as “with caution for concomitant use” (bile acid
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44
45 preparations such as ursodeoxycholic acid and chenodeoxycholic acid,
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48 aluminium-containing antacids such as sucralfate hydrate, aldioxa, etc., cholestyramine,
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50
51 cholestimid, digoxin, dabigatran etexylate methanesulfonate, and midazolam; other
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53
54 medicines or investigational drugs being used in clinical trials; non-internal therapy for
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57 constipation such as biofeedback therapy; disimpaction; and Duodopa® pump therapy.
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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

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6 registration at Visit 2, subjective symptoms and objective findings, medical history and
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9 complications, physical examinations, and vital signs will be recorded for the eligible
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11
12 patients. Subjective symptoms and objective findings will be collected twice more at
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15 Visits 3 and 4. Physical examinations and vital signs will also be recorded at Visit 4.
16
17 The JPAC-QOL,[18] MDS-UPDRS,[19] PDQ-39,[20] and EQ-5D-5L21,[22] surveys
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19 and laboratory measurements (haematology and blood chemistry) will be recorded at
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21
22 Visits 2 and 4 (Figure 2).
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27 Each patient will receive a Bowel Movement Diary at Visit 1 and will then record daily
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29 the status of bowel movements (date, stool hardness based on the Bristol scale,[17] and
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31 sensation of incomplete evacuation), use of rescue medication (date, dose of bisacodyl
32
33 suppositories) and concomitant medication (drugs for treatment of PD-related motor
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35 symptoms; date, drug name, dose), and treatment with non-investigational drugs and/or
36
37 therapy for constipation. If the patient enters the treatment period, he/she will continue
38
39 to record those items and also record daily use of the investigational drug (elobixibat or
40
41 placebo; date and dose, i.e. number of tablets taken) in the Diary starting at Visit 2 up to
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43 the end of study (Visit 4). Discontinuation, if it occurs, should also be recorded in the
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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

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7 Based on the efficacy assessment of elobixibat vs. placebo in phase 2 and phase 3
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9 clinical trials conducted in Japanese patients with chronic constipation,[28-30] we
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11
12 estimated a sample size of 40 patients for each group for 90% detection power at a
13
14
15 two-sided significance level of 5%. Assuming a dropout rate of 20%, we plan to recruit
16
17
18 100 PD patients with chronic constipation in this study.

19
20
21 The full analysis set (FAS) is defined as the randomised population receiving at least
22
23
24 one dose of the investigational drug with any measurement with regard to efficacy
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26
27 assessment. To ensure the robustness of study results, we also define a per-protocol set
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29
30 (PPS) as the population after the patients are excluded from the FAS due to any of the
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33 following reasons: any of the inclusion criteria inapplicable or any of the exclusion
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36 criteria applicable; a patient receiving the investigational drug with a non-allocated drug
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39 number; a patient receiving prohibited concomitant medications or therapies; a patient
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42 deemed to be inappropriate for study participation due to low drug compliance, lost to
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45 follow-up, lack of measurements, etc. The safety analysis set is defined as a population
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48 receiving at least one dose of the investigational drug after randomization.

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51 Continuous variables and categorical variables will be presented as means±standard
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54 deviation (SD) and as frequencies and percentages, respectively. Summary statistics
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56
57 may include medians and quartiles, as appropriate. Comparisons will be made for
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6 primary outcomes between the elobixibat group and the placebo group by analysis of
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9 covariance (ANCOVA) using baseline values and sex as covariates. Adjusted means
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12 with 95% confidence intervals and p values will be presented at a two-sided
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14
15 significance level of 5%. Within-group variations will be assessed by paired *t*-tests.
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18 Missing values will be imputed by the last observation carried forward (LOCF) method.
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21 Safety data will be shown as frequencies and percentages by group and individual event.
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27 **PATIENT AND PUBLIC INVOLVEMENT**

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30 No formal patient advisory committee was established, and there was no patient or
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33 public involvement in the design and planning of the study.
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38 **ETHICS AND DISSEMINATION**

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41 This study will be conducted according to the protocol that has been prepared in
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44 accordance with the Helsinki Declaration, Clinical Trials Act of the Japan Ministry of
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47 Health, Labour and Welfare, and related laws and regulations. Each study patient will
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50 be anonymously identified by a specific identification code and hence protected against
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53 privacy invasion. The information and data of each patient will be used exclusively for
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56 the study purpose and will never be disseminated outside the study.
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6 As a coordinating centre, SRD Co., Ltd. will share necessary information related to this
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9 study at the participating medical organizations in this study, conduct operations aimed
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12 at facilitating this study, and provide support to investigators.
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15 Data management and monitoring are conducted by Juntendo Clinical Research and
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18 Trial Center, Juntendo University Hospital. Details are specified in the Data
19
20
21 Management Plan and Monitoring Plan.
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24 If a serious health hazard arises due to participation in this study, coverage benefits can
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27 be received from insurance carried by a principal investigator, provided, however, that
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30 compensation may be reduced or not compensated if it is proven that the health hazard
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33 was caused by the research subject's own wilful act or gross negligence. In addition, if
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36 there is no causal relationship between the newly occurring health hazard and the
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39 deterioration of the originally affected disease, it is not covered by compensation. After
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42 completion of the study by each research subject, the investigators will make efforts to
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44
45 provide the best medical care obtained from the results of the research.
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51 **DISCUSSION AND DISSEMINATION**

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54 PD treatment is usually focused on the amelioration of movement dysfunction.
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57 However, patients with PD have many non-motor symptoms, especially autonomic
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6 dysfunction. Chronic constipation has been considered one of the troublesome
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8 symptoms affecting the QOL of PD patients, and it may even be life-threatening.
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11 Although fermented milk products containing probiotics and prebiotic fibres may have a
12
13 favourable effect on PD-related constipation, they will not be available as laxatives.
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15

16
17 Although multiple classes of laxatives are available, there is little evidence supporting
18
19 their use for PD-related constipation. An evidence-based medicine review[1]
20
21 recommends only three drugs/foods for PD-related constipation, including macrogol,
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23 lubiprostone, and probiotics/prebiotic fibres. Two laxatives are considered “likely
24
25 efficacious” and “possibly useful” for the treatment of constipation in PD patients based
26
27 on the quality of randomised, controlled trials. We believe the randomised, clinical
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29 study proposed here will be useful for expanding treatment options for PD-related
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31 constipation in an evidence-based manner.
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42 The study findings will be presented at relevant conferences and published in a
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44 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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6 study conduct. It should be noted that the two companies and their employees will never
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8
9 be involved in any study procedures including collection, analysis or interpretation of
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12 data, ensuring (sub)investigators will be completely independent of the funders
13
14
15 throughout study conduct.
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21 **Competing interests**

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24 There are no competing interests.
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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

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Figure 1

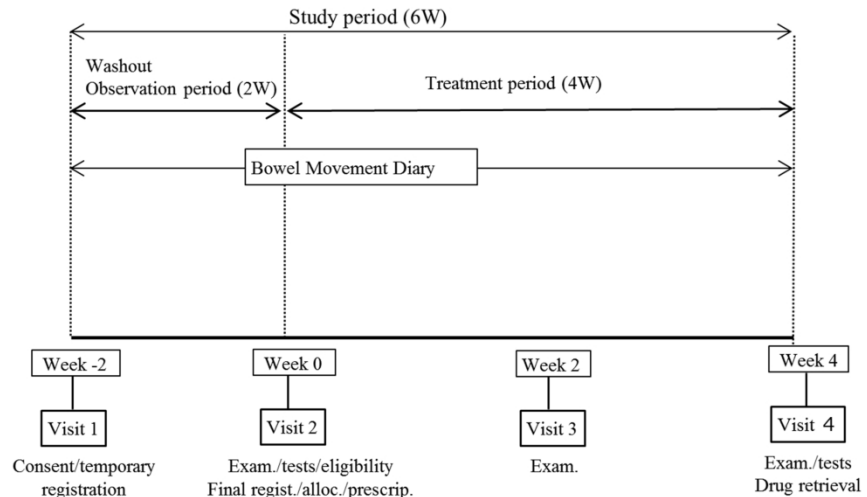


Figure 1 Study outline

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)		
	Patient background	○			
	Subjective symptoms/objective findings		○	○	○
Physical examinations	History/complications	○	○		
	Physical examinations	○	○		○
	Vital signs (blood pressure/pulse rate)		○		○
	Use of investigational medication		←	→	→
Bowel Movement Diary	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)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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 ___

1 Introduction

2			
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention
5			
6		6b	Explanation for choice of comparators
7			
8	Objectives	7	Specific objectives or hypotheses
9			
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial or single group),
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
12			

14 Methods: Participants, interventions, and outcomes

15			
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will
17			be collected. Reference to where list of study sites can be obtained
18			
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)
21			
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be
23			administered
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose
25			change in response to harms, participant request, or improving/worsening disease)
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence
27			(eg, drug tablet return, laboratory tests)
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
29			
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,
32			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen
33			efficacy and harm outcomes is strongly recommended
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for
35			participants. A schematic diagram is highly recommended (see Figure)
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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including
2 clinical and statistical assumptions supporting any sample size calculations _____ 19-21 _____

3
4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____ 19-21 _____

6
7 **Methods: Assignment of interventions (for controlled trials)**

8 Allocation:

9
10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any
11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
13 or assign interventions _____ 13-15 _____

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16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered,
17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
18 mechanism _____ 13-15 _____

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20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to
21 interventions _____ 13-15 _____

22
23 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome
24 assessors, data analysts), and how _____ 13-15 _____

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27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's
28 allocated intervention during the trial _____ 13-15 _____

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31 **Methods: Data collection, management, and analysis**

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33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related
34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
36 Reference to where data collection forms can be found, if not in the protocol _____ 19-21 _____

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39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be
40 collected for participants who discontinue or deviate from intervention protocols _____ 19-21 _____

1	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 ___
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5	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 ___
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ 8, 9 ___
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)	___ 19-21 ___
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13				
14	Methods: Monitoring			
15				
16	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 ___
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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 ___
23				
24				
25	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 ___
26				
27				
28	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 ___
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 21, 22 ___
35				
36				
37	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 ___
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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6				
7	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
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	34, 35
11				
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13	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
14				
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16	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
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20	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
21				
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	34
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
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28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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33				
34	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
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36				

*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](https://creativecommons.org/licenses/by/4.0/)" 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

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7 **Protocol: A multicentre, placebo-controlled, randomised, double-blind,**
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9 **parallel-group study investigating the efficacy and safety of elobixibat, an ileal bile**
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11 **acid transporter inhibitor, in patients with Parkinson's disease with chronic**
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13 **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]

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6 Recently, in addition to existing osmotic agents (macrogol 4000 often in combination
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9 with electrolytes, movicol, lactulose), new classes of laxatives have been developed for
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12 chronic constipation, including epithelial function transformation drugs (lubiprostone,
13
14
15 linaclotide) and an ileal bile acid transporter (IBAT) inhibitor (elobixibat).
16

17
18 However, the evidence for the effectiveness of laxatives either conventional or recently
19
20
21 developed for the treatment of chronic constipation in PD patients is not extensive,
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23
24 except for macrogol and lubiprostone, a chloride channel-2 activator, which have been
25
26
27 shown to be significantly efficacious over placebo in improving bowel movement
28
29
30 frequency.[10, 11] Although probiotics and prebiotic fibre were also proposed to be
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32
33 useful for the treatment of PD-related constipation,[12, 13] more evidence for different
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35
36 classes of laxatives is needed to expand therapeutic options for chronic constipation in
37
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39 PD patients.
40

41
42 Elobixibat is an inhibitor of IBAT, which is expressed in the distal ileum. Bile acids
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44
45 escape the reabsorption process via the action of this drug and then enter the large
46
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48 intestinal lumen.[14] The increased levels of bile acids may interact with
49
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51 transmembrane G-protein-coupled receptor (TGR5) molecules, leading to an influx of
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54 water and electrolytes into the lumen. The bile acid-TGR5 interaction also triggers
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57 serotonin release into the intestinal wall, which activates intrinsic primary afferent
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6 neurons. This leads to an interneuron-mediated activation of motor neurons that finally
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9 activates large-intestinal motility,[15] inducing colonic high-amplitude propagated
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12 contractions.[16] Recently, a large-scale, multicenter, randomized, double-blind phase 3
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14
15 study was conducted, revealing that elobixibat resolved idiopathic chronic constipation
16
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18 with no serious safety concerns.[17] Elobixibat is thus expected to be a novel option for
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20
21 the treatment of chronic constipation on the basis of its mode of action being totally
22
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24 different from those of the other existing laxatives.[18, 19]

25
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27 We are planning to conduct a study to examine the efficacy and safety of elobixibat in
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30 PD patients with chronic constipation. The superiority of elobixibat over placebo will be
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33 explored in a randomized, double-blind, comparative study during 4-week daily
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36 administration of the drug to eligible patients. The drug will also be evaluated for its
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39 safety and potential impact on the underlying PD condition. The study methodology is
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42 detailed in this article.
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47 **METHODS AND ANALYSIS**

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

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6 Parkinson's Disease Questionnaire-39 (PDQ-39),[23] and Euro-Qol 5 dimension – 5
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9 level (EQ-5D-5L)[24,25] will be assessed. The use of dopamine preparations will also
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11
12 be monitored, since the effectiveness of elobixibat in improving constipation via
13
14
15 increased levels of intestinal bile acids may also improve small intestinal absorption of
16
17
18 the anti-Parkinsonian medications.
19

20
21 Subgroup analyses will be further performed for these endpoints by the presence or
22
23
24 absence of complications, age (\geq or $<$ 65 years), Hoehn and Yahr scale (1 to 4), duration
25
26
27 of the underlying disease (PD; \geq or $<$ median), dose equivalence of L-Dopa prior to
28
29
30 elobixibat initiation, and duration of chronic constipation (\geq or $<$ 20 years).
31
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36 **Overall study design**

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39 This study is designed as a multicentre, randomised, double-blind, placebo-controlled,
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41
42 parallel-group study at 3 academic centres (Juntendo University Hospital, Juntendo
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44
45 University Urayasu Hospital, and Juntendo University Nerima Hospital), in which PD
46
47
48 patients with chronic constipation will pre-prandially receive elobixibat (Goofice®; EA
49
50
51 Pharma Co., Ltd., Tokyo, Japan) or its indistinguishable matched placebo once daily for
52
53
54 four weeks, and the frequency of spontaneous bowel movements will be compared
55
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57 between the patients receiving either elobixibat or placebo. Safety information,
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6 including adverse events (AEs) and discontinuation and interruption of the
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9 investigational drugs, will also be collected.
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12 The study will consist of two periods, the observation period and the treatment period. It
13
14 will be conducted from October 26, 2020 (date of the first announcement in the Japan
15
16 Registry of Clinical Trials; jRCT) through September 30, 2022. As seen in Figure 1, we
17
18 plan two steps for patient registration, temporary and final. At Week -2 (Visit 1) of the
19
20 observation period, PD patients will be provided with the detailed information about the
21
22 study. After providing written, informed consent for study participation, they will be
23
24 temporarily registered based on the patient definitions (see below). Following the
25
26 observation period, the patients will be further assessed for study participation at Week
27
28 0 (Visit 2). Once none of the exclusion criteria are confirmed to be applicable, the
29
30 patients will be finally registered and assigned to either the elobixibat group or the
31
32 placebo group in a double-blind manner (Figure 1). The eligible patients will visit their
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34 clinical sites twice more (Visit 3 at Week 2 and Visit 4 at Week 4) during the 4-week
35
36 treatment period.
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51 A Bowel Movement Diary will be provided at Week -2 (Visit 1, see below) to each
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53 patient, once temporarily registered. The patient will record drug use, bowel movements,
54
55 etc. in the Diary daily throughout the study period.
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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

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6 dysfunction; has malignant tumour(s); has a history of hypersensitivity to elobixibat; is
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9 taking bile acid preparations (ursodeoxycholic acid, chenodeoxycholic acid),
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12 aluminium-containing preparations (sucralfate hydrate, aldioxa, etc.), cholestyramine,
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15 colestimide, digoxin, dabigatran etexilate mesylate, or midazolam; has a Mini–Mental
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18 State Examination (MMSE) score^[30] ≤ 26 ; or is considered ineligible by the
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20
21 investigator or sub-investigator, hereinafter termed (sub)investigator, for study
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24 participation because of safety concerns, poor protocol compliance, etc. Female patients
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26
27 will also be excluded if they are pregnant, breastfeeding, or expecting pregnancy during
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29
30 the study period.

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33 Patient exclusion is further scheduled at the final registration if one of the following
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36 cases applies to a patient during the 2-week observation period: use of the rescue
37
38
39 medication (bisacodyl 10 mg suppositories) ≥ 5 times; use of the rescue medication
40
41
42 within 72 hours post-bowel movement; experience of spontaneous bowel movement
43
44
45 with mushy or watery stool according to Bristol Stool Form Scale type 6 or 7;^[20] or
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47
48 use of prohibited medications/therapies (see below).

54 **Study procedures and schedule**

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57 Registration of study patients and their allocation to the investigational drug will be
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6 performed via an internet-mediated Interactive Web Response System (IWRS). The
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9 (sub)investigator (or study-assigned coordinator) will access the specific website for
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11
12 patient registration and allocation using a specific ID and password, and complete the
13
14
15 necessary information about each anonymized patient. Investigational drug allocation
16
17
18 will be instantly presented for each patient following eligibility judgment (see below).
19

20
21 The schedule of this study is shown in Figure 2.
22

23
24 The (sub)investigator will give detailed explanations of this study to each PD patient
25
26
27 who meets the inclusion criteria but not the exclusion criteria at Visit 1 and then obtain
28
29
30 the patient's written, informed consent on a free will basis. The patient will be informed
31
32
33 that he/she may withdraw his/her consent for any reason and at any time during the
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36 study period. The (sub)investigator will give the eligible patient a temporary
37
38
39 identification code and enter the patient's background in the Eligibility for Temporary
40
41
42 Registration form of the electronic Case Report Form (eCRF; see Figures 1 and 2).
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44

45 The Bowel Movement Diary and rescue medication (bisacodyl 10 mg suppositories)
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47
48 will be provided to each patient at temporary registration. The (sub)investigator will
49
50
51 instruct each patient how to complete the required items in the Diary.
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54 At Visit 2, the (sub)investigator will judge the eligibility of each patient for final
55
56
57 registration referring to the exclusion criteria (see above) and enter the background of
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6 qualified patients in the Eligibility for Final Registration form of the eCRF. Once the
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9 patient's eligibility is confirmed, a final identification code will be assigned to the
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11
12 patient, who will be then allocated randomly to treatment group.

13
14
15 Drug allocation will be based on a stratified, permuted block method with sex as an
16
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18 allocation factor. Satt Co., Ltd. (Tokyo) will perform the allocation by preparing a drug
19
20
21 allocation table using IWRS. The study drugs will be sealed with specific drug numbers
22
23
24 and delivered to the individual institutional sites according to the allocation table. At the
25
26
27 final registration of patients, the (sub)investigator will check the final identification
28
29
30 code and the specific number of randomly allocated investigational drug for each
31
32
33 qualified patient on the IWRS screen. The specifically numbered drug will be provided
34
35
36 to the patient by the (sub)investigator at Visit 2 and Visit 3 for 2 weeks each time (3
37
38
39 tablets x 14 days), as described below. The key code of the allocation table will be
40
41
42 opened by Satt after all study data has been locked.

43
44
45 The patient will start the 4-week treatment period with once-daily, preprandial intake of
46
47
48 2 tablets of investigational drug (elobixibat 10 mg) or its placebo. One tablet may be
49
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51 added on the next day if no spontaneous bowel movement is observed during the next
52
53
54 24 hours. If excessive effectiveness or discomfort appears, the dosage may be decreased
55
56
57 at the direction of the (sub)investigator or the patient's judgment. Dose augmentation
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6 from 1 tablet to 3 tablets will not be allowed. Interruption of the investigational drug
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8
9 due to the occurrence of an AE may be allowed at the direction of the (sub)investigator
10
11
12 or the patient's judgment, but as-needed intake of the drug based on bowel movement
13
14
15 status will not be acceptable. The drug may be restarted at the dose taken immediately
16
17
18 before interruption or at a lower dose. Inappropriately long (≥ 7 consecutive days) or
19
20
21 frequent (≥ 3 days per week during 2 consecutive weeks) interruption of the drug may
22
23
24 lead to discontinuation of the patient from the study at the (sub)investigator's discretion.
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30 **Rescue and concomitant medications/therapies**

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33 Since this study is primarily planned to explore the efficacy and safety of elobixibat as a
34
35
36 laxative in PD patients, concomitant medications will be used throughout the study
37
38
39 period for parkinsonism except for Duodopa[®] pump therapy (Abbvie Inc., North
40
41
42 Chicago, IL, USA) with levodopa/carbidopa hydrate intestinal gel. Bisacodyl 10 mg
43
44
45 suppositories may be used once to twice daily as a rescue medication when no bowel
46
47
48 movement is observed for 72 or more consecutive hours, unless emergency use is
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51 required.
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54 Because of potential effects on the study results and/or interpretation thereof, use of the
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57 following drugs or therapies as concomitant medications will be prohibited throughout
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6 the entire study period: laxatives other than elobixibat such as magnesium hydroxide,
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8
9 sodium picosulphate, sennosides, lubiprostone, linaclotide, polyethylene glycol
10
11
12 (macrogol 4000), etc.; oriental medicines for constipation (daiokanzoto extract,
13
14
15 choijokito extract, daisaikoto extract, etc.); medicines indicated for irritable bowel
16
17
18 syndrome (IBS; ramosetron hydrochloride, polycarbophil calcium, trimebutine maleate,
19
20
21 etc.); supplements or over-the-counter drugs to improve the constipated condition;
22
23
24 enema or intestinal lavage; lavage solution for colonoscopy; drugs listed in the
25
26
27 Precaution section of the package insert of elobixibat (Goofice® 5 mg tablets) as “with
28
29
30 caution for concomitant use” (bile acid preparations such as ursodeoxycholic acid and
31
32
33 chenodeoxycholic acid, aluminium-containing antacids such as sucralfate hydrate,
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35
36 aldioxa, etc., cholestyramine, cholestimid, digoxin, dabigatran etexylate
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38
39 methanesulfonate, and midazolam; other medicines or investigational drugs being used
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41
42 in clinical trials; non-internal therapy for constipation such as biofeedback therapy;
43
44
45 disimpaction; and Duodopa® pump therapy. The patient should self-report in his/her
46
47
48 Bowel Movement Diary when any of the drugs/agents/therapies listed above are used.
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54 **Discontinuation of the study**

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56
57 Participation of a recruited patient will be discontinued if any of the following
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6 conditions is met: judged difficult to continue due to the onset of an AE; ineligibility
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8
9 confirmed after study initiation; lost to follow-up; confirmed or suspected pregnancy;
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11
12 voluntary withdrawal; repeated protocol violations; or any other reason for which the
13
14
15 (sub)investigator judges that discontinuation would be necessary.
16

17
18 All study procedures will be discontinued if any of the following conditions is met: the
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20
21 Institutional Review Board of Juntendo University Hospital determines that the study
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23
24 should be discontinued; the appearance of safety concerns with potential impact on
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27 study progress; appearance of incidents or information that may potentially lead to
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29
30 impairment of ethical or scientific validity of the study; or appearance of any other
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33 incidents or information that may potentially lead to impairment of appropriateness of
34
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36 study conduct and/or reliability of study results.
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43 **Observations and measurements**

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45 Patient background, medical history and complications, and data of physical
46
47
48 examinations will be collected at Visit 1 (Figure 2). On final judgment regarding study
49
50
51 registration at Visit 2, subjective symptoms and objective findings, medical history and
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53
54 complications, physical examinations, and vital signs will be recorded for the eligible
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57 patients. Subjective symptoms and objective findings will be collected twice more at
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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,

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6 impairments, deaths, infections, laboratory abnormalities, and symptoms.
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9 The (sub)investigator will examine the patient for AEs throughout the study period
10
11 (Figure 2) and upon finding an event, record in the patient's eCRF its: name; onset date;
12
13 severity (mild, moderate, or severe); seriousness (non-serious or serious); defined
14
15 category of seriousness (death, life-threatening, hospitalization-initial or prolonged,
16
17 disability or permanent damage, an event potentially leading to disability or permanent
18
19 damage, ill condition judged as serious in reference to the aforementioned categories, or
20
21 congenital anomaly or birth defect); predictability (known or unknown); action taken
22
23 regarding the investigational drug (continuation, interruption, or discontinuation);
24
25 outcome (recovered, improving, not recovered, recovered with sequelae, died, or
26
27 unknown); date of outcome; causal relationship with use of the investigational drug
28
29 ('not related' or grades other than 'not related'; suspected factor(s) other than the
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31 investigational drug should be recorded if judged 'not related').
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48 **Study population and statistical analysis**

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51 Based on the efficacy assessment of elobixibat vs. placebo in phase 2 and phase 3
52
53 clinical trials conducted in Japanese patients with chronic constipation,[17,31,32] the
54
55 expected effect size was calculated as 3.06 (5.66 for elobixibat 10 mg vs. 2.60 for
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6 placebo) with a common standard deviation of 4.15. Accordingly, we estimated a
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8
9 sample size of 40 patients for each group for 90% detection power at a two-sided
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11
12 significance level of 5%. Assuming a dropout rate of 20%, we plan to recruit 100 PD
13
14
15 patients with chronic constipation in this study.
16

17
18 The full analysis set (FAS) is defined as the randomised population receiving at least
19
20
21 one dose of the investigational drug with any measurement with regard to efficacy
22
23
24 assessment. To ensure the robustness of study results, we also define a per-protocol set
25
26
27 (PPS) as the population after the patients are excluded from the FAS due to any of the
28
29
30 following reasons: any of the inclusion criteria inapplicable or any of the exclusion
31
32
33 criteria applicable; a patient receiving the investigational drug with a non-allocated drug
34
35
36 number; a patient receiving prohibited concomitant medications or therapies; a patient
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38
39 deemed to be inappropriate for study participation due to low drug compliance, lost to
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41
42 follow-up, lack of measurements, etc. The safety analysis set is defined as a population
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44
45 receiving at least one dose of the investigational drug after randomization.
46
47

48
49 Continuous variables and categorical variables will be presented as mean±standard
50
51
52 deviation (SD) and as frequencies and percentages, respectively. Summary statistics
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54
55 may include medians and quartiles, as appropriate. Comparisons will be made for
56
57
58 primary outcomes between the elobixibat group and the placebo group by analysis of
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6 covariance (ANCOVA) using baseline values and sex as covariates. Adjusted means
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8
9 with 95% confidence intervals and p values will be presented at a two-sided
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11
12 significance level of 5%. Within-group variations will be assessed by paired *t*-tests.
13
14
15 Missing values will be imputed by the last observation carried forward (LOCF) method.
16
17
18 Safety data will be shown as frequencies and percentages by group and individual event.
19
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24 **PATIENT AND PUBLIC INVOLVEMENT**

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26
27 No formal patient advisory committee was established, and there was no patient or
28
29
30 public involvement in the design and planning of the study.
31
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34

35 **ETHICS AND DISSEMINATION**

36
37
38 This study will be conducted according to the protocol that has been prepared in
39
40
41 accordance with the Helsinki Declaration, Clinical Trials Act of the Japan Ministry of
42
43
44 Health, Labour and Welfare, and related laws and regulations. Each study patient will
45
46
47 be anonymously identified by a specific identification code and hence protected against
48
49
50 privacy invasion. The information and data of each patient will be used exclusively for
51
52
53 the study purpose and will never be disseminated outside the study.
54
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56 As a coordinating centre, SRD Co., Ltd. will share necessary information related to this
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6 study at the participating medical organizations in this study, conduct operations aimed
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8
9 at facilitating this study, and provide support to investigators. Data management and
10
11
12 monitoring are conducted by Juntendo Clinical Research and Trial Center, Juntendo
13
14
15 University Hospital. Details are specified in the Data Management Plan and Monitoring
16
17
18 Plan.

19
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21 If a serious health hazard arises due to participation in this study, coverage benefits can
22
23
24 be received from insurance carried by a principal investigator, provided, however, that
25
26
27 compensation may be reduced or not compensated if it is proven that the health hazard
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30 was caused by the research subject's own wilful act or gross negligence. In addition, if
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33 there is no causal relationship between the newly occurring health hazard and the
34
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36 deterioration of the originally affected disease, it is not covered by compensation. After
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39 completion of the study by each research subject, the investigators will make efforts to
40
41
42 provide the best medical care obtained from the results of the research.

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

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6 decreased colonic motility, reflex inability of the pelvic floor muscles during attempted
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9 defecation, and IBS.[2,6] However, the precise mechanisms underlying constipation
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12 remain unknown. Thus, the same treatment algorithm used in patients with idiopathic
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15 chronic constipation should be recommended for constipation occurring in the patients
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18 with PD.[2] Elobixibat is a highly potent selective IBAT inhibitor that results in excess
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21 bile acids in the colon, which is associated with increased water influx from the colon
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23
24 and colon motility via an interaction with TGR5.[15] These action mechanisms produce
25
26
27 favourable effects on idiopathic chronic constipation and IBS.[17] Considering the
28
29
30 effectiveness of macrogol and lubiprostone against PD-accompanying constipation,
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32
33 elobixibat is also expected to improve this condition. This study will provide the first
34
35
36 evidence of whether elobixibat is a useful treatment for chronic constipation in patients
37
38
39 with PD, as has already been demonstrated for idiopathic chronic constipation.
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45 We believe the randomised, clinical study proposed here will be useful for expanding
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48 treatment options for PD-related constipation in an evidence-based manner.
49

50
51 The study findings will be presented at relevant conferences and published in a
52
53
54 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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6 study conduct. It should be noted that the two companies and their employees will never
7
8
9 be involved in any study procedures including collection, analysis or interpretation of
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12 data, ensuring (sub)investigators will be completely independent of the funders
13
14
15 throughout study conduct.
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21 **Competing interests**

22
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24 There are no competing interests.
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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

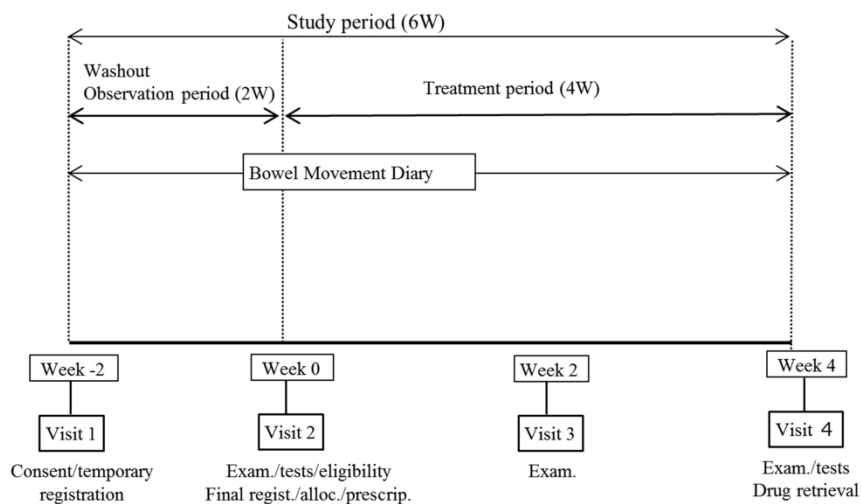


Figure 1 Study outline

254x190mm (307 x 307 DPI)

Figure 2

Visit	Observation period		Administration start		Treatment period	
	Visit 1	Visit 2	Visit 3	Visit 4	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)				
Patient background	○					
Subjective symptoms/objective findings			○			○
Physical examinations						
History/complications	○	○				
Physical examinations	○	○				○
Vital signs (blood pressure/pulse rate)		○				○
Use of investigational medication			←		→	
Use of rescue/concomitant medication	←				→	
Bowel Movement Diary			←		→	
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)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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 ___

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1	Introduction			
2				
3	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 __
4				
5				
6		6b	Explanation for choice of comparators	__ NA __
7				
8	Objectives	7	Specific objectives or hypotheses	__ 6-8 __
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial or single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__ 6-8, 10, 11 __
11				
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	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 __
17				
18				
19	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 __
20				
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__ 10, 11 __
23				
24				
25				
26		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 __
27				
28				
29		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__ 13-15 __
30				
31				
32		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__ 13-17 __
33				
34	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 __
35				
36				
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38				
39				
40	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 __
41				
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1	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 ___
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___ 19-21 ___
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

8				
9				
10	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 ___
11				
12				
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15				
16	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 ___
17				
18				
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___ 13-15 ___
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___ 13-15 ___
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___ 13-15 ___
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

32				
33	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 ___
34				
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39		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 ___
40				
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42				

1	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 ___
2				
3				
4				
5	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 ___
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ 8, 9, 10 ___
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 ___
11				
12				
13				
14	Methods: Monitoring			
15				
16	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 ___
17				
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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	___ 17,18 ___
23				
24				
25	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 ___
26				
27				
28	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 ___
29				
30				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 22, 23 ___
35				
36				
37	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 ___
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
5				
6				
7	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
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	34, 35
11				
12				
13	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
14				
15				
16	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
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19				
20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	26
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	34
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Material
32				
33				
34	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
35				
36				

*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)

Journal:	<i>BMJ Open</i>
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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

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7 **Protocol: A multicentre, placebo-controlled, randomised, double-blind,**
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9 **parallel-group study investigating the efficacy and safety of elobixibat, an ileal bile**
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11 **acid transporter inhibitor, in patients with Parkinson's disease with chronic**
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13 **constipation (CONST-PD)**
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21 Taku Hatano¹, Genko Oyama¹, Yasushi Shimo², Kotaro Ogaki³, Noriko Nishikawa¹,
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For peer review only

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]

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6 Recently, in addition to existing osmotic agents (macrogol 4000 often in combination
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9 with electrolytes, movicol, lactulose), new classes of laxatives have been developed for
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12 chronic constipation, including epithelial function transformation drugs (lubiprostone,
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15 linaclotide) and an ileal bile acid transporter (IBAT) inhibitor (elobixibat).
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18 However, the evidence for the effectiveness of laxatives either conventional or recently
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21 developed for the treatment of chronic constipation in PD patients is not extensive,
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24 except for macrogol and lubiprostone, a chloride channel-2 activator, which have been
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27 shown to be significantly efficacious over placebo in improving bowel movement
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30 frequency.[10, 11] Although probiotics and prebiotic fibre were also proposed to be
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33 useful for the treatment of PD-related constipation,[12, 13] more evidence for different
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36 classes of laxatives is needed to expand therapeutic options for chronic constipation in
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39 PD patients.
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42 Elobixibat is an inhibitor of IBAT, which is expressed in the distal ileum. Bile acids
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45 escape the reabsorption process via the action of this drug and then enter the large
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48 intestinal lumen.[14] The increased levels of bile acids may interact with
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51 transmembrane G-protein-coupled receptor (TGR5) molecules, leading to an influx of
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54 water and electrolytes into the lumen. The bile acid-TGR5 interaction also triggers
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57 serotonin release into the intestinal wall, which activates intrinsic primary afferent
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6 neurons. This leads to an interneuron-mediated activation of motor neurons that finally
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9 activates large-intestinal motility,[15] inducing colonic high-amplitude propagated
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12 contractions.[16] Recently, a large-scale, multicenter, randomized, double-blind phase 3
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15 study was conducted, revealing that elobixibat resolved idiopathic chronic constipation
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18 with no serious safety concerns.[17] Elobixibat is thus expected to be a novel option for
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21 the treatment of chronic constipation on the basis of its mode of action being totally
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24 different from those of the other existing laxatives.[18, 19]

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

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

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6 Parkinson's Disease Questionnaire-39 (PDQ-39),[23] and Euro-Qol 5 dimension – 5
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9 level (EQ-5D-5L)[24,25] will be assessed. The use of dopamine preparations will also
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11
12 be monitored, since the effectiveness of elobixibat in improving constipation via
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15 increased levels of intestinal bile acids may also improve small intestinal absorption of
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18 the anti-Parkinsonian medications.
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21 Subgroup analyses will be further performed for these endpoints by the presence or
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24 absence of complications, age (\geq or $<$ 65 years), Hoehn and Yahr scale (1 to 4), duration
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27 of the underlying disease (PD; \geq or $<$ median), dose equivalence of L-Dopa prior to
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30 elobixibat initiation, and duration of chronic constipation (\geq or $<$ 20 years).
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36 **Overall study design**

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39 This study is designed as a multicentre, randomised, double-blind, placebo-controlled,
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42 parallel-group study at 3 academic centres (Juntendo University Hospital, Juntendo
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45 University Urayasu Hospital, and Juntendo University Nerima Hospital), in which PD
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48 patients with chronic constipation will pre-prandially receive elobixibat (Goofice®; EA
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51 Pharma Co., Ltd., Tokyo, Japan) or its indistinguishable matched placebo once daily for
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54 four weeks, and the frequency of spontaneous bowel movements will be compared
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57 between the patients receiving either elobixibat or placebo. Safety information,
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6 including adverse events (AEs) and discontinuation and interruption of the
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9 investigational drugs, will also be collected.
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12 The study will consist of two periods, the observation period and the treatment period. It
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14 will be conducted from October 26, 2020 (date of the first announcement in the Japan
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16 Registry of Clinical Trials; jRCT) through September 30, 2022. As seen in Figure 1, we
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18 plan two steps for patient registration, temporary and final. At Week -2 (Visit 1) of the
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20 observation period, PD patients will be provided with detailed information about the
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22 study. After providing written, informed consent for study participation, they will be
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24 temporarily registered based on the patient definitions (see below). Following the
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26 observation period, the patients will be further assessed for study participation at Week
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28 0 (Visit 2). Once none of the exclusion criteria are confirmed to be applicable, the
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30 patients will be finally registered and assigned to either the elobixibat group or the
31
32 placebo group in a double-blind manner (Figure 1). The eligible patients will visit their
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34 clinical sites twice more (Visit 3 at Week 2 and Visit 4 at Week 4) during the 4-week
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36 treatment period.
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51 A Bowel Movement Diary will be provided at Week -2 (Visit 1, see below) to each
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53 patient, once temporarily registered. The patient will record drug use, bowel movements,
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55 etc. in the Diary daily throughout the study period.
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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

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

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33 Patient exclusion is further scheduled at the final registration if one of the following
34
35
36 cases applies to a patient during the 2-week observation period: use of the rescue
37
38
39 medication (bisacodyl 10 mg suppositories) ≥ 5 times; use of the rescue medication
40
41
42 within 72 hours post-bowel movement; experience of spontaneous bowel movement
43
44
45 with mushy or watery stool according to Bristol Stool Form Scale type 6 or 7;^[20] or
46
47
48 use of prohibited medications/therapies (see below).

54 **Study procedures and schedule**

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56
57 Registration of study patients and their allocation to the investigational drug will be
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5
6 performed via an internet-mediated Interactive Web Response System (IWRS). The
7
8
9 (sub)investigator (or study-assigned coordinator) will access the specific website for
10
11
12 patient registration and allocation using a specific ID and password, and complete the
13
14
15 necessary information about each anonymized patient. Investigational drug allocation
16
17
18 will be instantly presented for each patient following eligibility judgment (see below).
19

20
21 The schedule of this study is shown in Figure 2.
22

23
24 The (sub)investigator will give detailed explanations of this study to each PD patient
25
26
27 who meets the inclusion criteria but not the exclusion criteria at Visit 1 and then obtain
28
29
30 the patient's written, informed consent on a free will basis. The patient will be informed
31
32
33 that he/she may withdraw his/her consent for any reason and at any time during the
34
35
36 study period. The (sub)investigator will give the eligible patient a temporary
37
38
39 identification code and enter the patient's background in the Eligibility for Temporary
40
41
42 Registration form of the electronic Case Report Form (eCRF; see Figures 1 and 2).
43
44

45 The Bowel Movement Diary and rescue medication (bisacodyl 10 mg suppositories)
46
47
48 will be provided to each patient at temporary registration. The (sub)investigator will
49
50
51 instruct each patient how to complete the required items in the Diary.
52

53
54 At Visit 2, the (sub)investigator will judge the eligibility of each patient for final
55
56
57 registration referring to the exclusion criteria (see above) and enter the background of
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6 qualified patients in the Eligibility for Final Registration form of the eCRF. Once the
7
8
9 patient's eligibility is confirmed, a final identification code will be assigned to the
10
11
12 patient, who will be then allocated randomly to treatment group.

13
14
15 Drug allocation will be based on a stratified, permuted block method with sex as an
16
17 allocation factor. Satt Co., Ltd. (Tokyo) will perform the allocation by preparing a drug
18
19 allocation table using IWRS. The study drugs will be sealed with specific drug numbers
20
21 and delivered to the individual institutional sites according to the allocation table. At the
22
23 final registration of patients, the (sub)investigator will check the final identification
24
25 code and the specific number of randomly allocated investigational drug for each
26
27 qualified patient on the IWRS screen. The specifically numbered drug will be provided
28
29 to the patient by the (sub)investigator at Visit 2 and Visit 3 for 2 weeks each time (3
30
31 tablets x 14 days), as described below. The key code of the allocation table will be
32
33 opened by Satt after all study data have been locked.
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45 The patient will start the 4-week treatment period with once-daily, preprandial intake of
46
47 2 tablets of investigational drug (elobixibat 10 mg) or its placebo. One tablet may be
48
49 added on the next day if no spontaneous bowel movement is observed during the next
50
51 24 hours. If excessive effectiveness or discomfort appears, the dosage may be decreased
52
53
54
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56
57 at the direction of the (sub)investigator or the patient's judgment. Dose augmentation
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6 from 1 tablet to 3 tablets will not be allowed. Interruption of the investigational drug
7
8
9 due to the occurrence of an AE may be allowed at the direction of the (sub)investigator
10
11
12 or the patient's judgment, but as-needed intake of the drug based on bowel movement
13
14
15 status will not be acceptable. The drug may be restarted at the dose taken immediately
16
17
18 before interruption or at a lower dose. Inappropriately long (≥ 7 consecutive days) or
19
20
21 frequent (≥ 3 days per week during 2 consecutive weeks) interruption of the drug may
22
23
24 lead to discontinuation of the patient from the study at the (sub)investigator's discretion.
25
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29

30 **Rescue and concomitant medications/therapies**

31
32
33 Since this study is primarily planned to explore the efficacy and safety of elobixibat as a
34
35
36 laxative in PD patients, concomitant medications will be used throughout the study
37
38
39 period for parkinsonism except for Duodopa[®] pump therapy (Abbvie Inc., North
40
41
42 Chicago, IL, USA) with levodopa/carbidopa hydrate intestinal gel. Bisacodyl 10 mg
43
44
45 suppositories may be used once to twice daily as a rescue medication when no bowel
46
47
48 movement is observed for 72 or more consecutive hours, unless emergency use is
49
50
51 required.
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54 Because of potential effects on the study results and/or interpretation thereof, use of the
55
56
57 following drugs or therapies as concomitant medications will be prohibited throughout
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6 the entire study period: laxatives other than elobixibat such as magnesium hydroxide,
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8
9 sodium picosulphate, sennosides, lubiprostone, linaclotide, polyethylene glycol
10
11
12 (macrogol 4000), etc.; oriental medicines for constipation (daiokanzoto extract,
13
14
15 choijokito extract, daisaikoto extract, etc.); medicines indicated for irritable bowel
16
17
18 syndrome (IBS; ramosetron hydrochloride, polycarbophil calcium, trimebutine maleate,
19
20
21 etc.); supplements or over-the-counter drugs to improve the constipated condition;
22
23
24 enema or intestinal lavage; lavage solution for colonoscopy; drugs listed in the
25
26
27 Precaution section of the package insert of elobixibat (Goofice® 5 mg tablets) as “with
28
29
30 caution for concomitant use” (bile acid preparations such as ursodeoxycholic acid and
31
32
33 chenodeoxycholic acid, aluminium-containing antacids such as sucralfate hydrate,
34
35
36 aldioxa, etc., cholestyramine, cholestimid, digoxin, dabigatran etexylate
37
38
39 methanesulfonate, and midazolam; other medicines or investigational drugs being used
40
41
42 in clinical trials; non-internal therapy for constipation such as biofeedback therapy;
43
44
45 disimpaction; and Duodopa® pump therapy. The patient should self-report in his/her
46
47
48 Bowel Movement Diary when any of the drugs/agents/therapies listed above are used.
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54 **Discontinuation of the study**

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56
57 Participation of a recruited patient will be discontinued if any of the following
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6 conditions is met: judged difficult to continue due to the onset of an AE; ineligibility
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8
9 confirmed after study initiation; lost to follow-up; confirmed or suspected pregnancy;
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12 voluntary withdrawal; repeated protocol violations; or any other reason for which the
13
14
15 (sub)investigator judges that discontinuation would be necessary.
16

17
18 All study procedures will be discontinued if any of the following conditions is met: the
19
20
21 Institutional Review Board of Juntendo University Hospital determines that the study
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23
24 should be discontinued; the appearance of safety concerns with potential impact on
25
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27 study progress; appearance of incidents or information that may potentially lead to
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29
30 impairment of ethical or scientific validity of the study; or appearance of any other
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32
33 incidents or information that may potentially lead to impairment of appropriateness of
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36 study conduct and/or reliability of study results.
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43 **Observations and measurements**

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45 Patient background, medical history and complications, and data of physical
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47
48 examinations will be collected at Visit 1 (Figure 2). On final judgment regarding study
49
50
51 registration at Visit 2, subjective symptoms and objective findings, medical history and
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53
54 complications, physical examinations, and vital signs will be recorded for the eligible
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57 patients. Subjective symptoms and objective findings will be collected twice more at
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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,

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6 impairments, deaths, infections, laboratory abnormalities, and symptoms.
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9 The (sub)investigator will examine the patient for AEs throughout the study period
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11 (Figure 2) and upon finding an event, record in the patient's eCRF its: name; onset date;
12
13 severity (mild, moderate, or severe); seriousness (non-serious or serious); defined
14
15 category of seriousness (death, life-threatening, hospitalization-initial or prolonged,
16
17 disability or permanent damage, an event potentially leading to disability or permanent
18
19 damage, ill condition judged as serious in reference to the aforementioned categories, or
20
21 congenital anomaly or birth defect); predictability (known or unknown); action taken
22
23 regarding the investigational drug (continuation, interruption, or discontinuation);
24
25 outcome (recovered, improving, not recovered, recovered with sequelae, died, or
26
27 unknown); date of outcome; causal relationship with use of the investigational drug
28
29 ('not related' or grades other than 'not related'; suspected factor(s) other than the
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31 investigational drug should be recorded if judged 'not related').
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48 **Study population and statistical analysis**

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51 Based on the efficacy assessment of elobixibat vs. placebo in phase 2 and phase 3
52
53 clinical trials conducted in Japanese patients with chronic constipation,[17,31,32] the
54
55 expected effect size was calculated as 3.06 (5.66 for elobixibat 10 mg vs. 2.60 for
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6 placebo) with a common standard deviation of 4.15. Accordingly, we estimated a
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8
9 sample size of 40 patients for each group for 90% detection power at a two-sided
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11
12 significance level of 5%. Assuming a dropout rate of 20%, we plan to recruit 100 PD
13
14
15 patients with chronic constipation in this study.
16

17
18 The full analysis set (FAS) is defined as the randomised population receiving at least
19
20
21 one dose of the investigational drug with any measurement with regard to efficacy
22
23
24 assessment. To ensure the robustness of study results, we also define a per-protocol set
25
26
27 (PPS) as the population after the patients are excluded from the FAS due to any of the
28
29
30 following reasons: any of the inclusion criteria inapplicable or any of the exclusion
31
32
33 criteria applicable; a patient receiving the investigational drug with a non-allocated drug
34
35
36 number; a patient receiving prohibited concomitant medications or therapies; a patient
37
38
39 deemed to be inappropriate for study participation due to low drug compliance, lost to
40
41
42 follow-up, lack of measurements, etc. The safety analysis set is defined as a population
43
44
45 receiving at least one dose of the investigational drug after randomization.
46
47

48
49 Continuous variables and categorical variables will be presented as mean±standard
50
51
52 deviation (SD) and as frequencies and percentages, respectively. Summary statistics
53
54
55 may include medians and quartiles, as appropriate. Comparisons will be made for
56
57
58 primary outcomes between the elobixibat group and the placebo group by analysis of
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6 covariance (ANCOVA) using baseline values and sex as covariates. Adjusted means
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8
9 with 95% confidence intervals and p values will be presented at a two-sided
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11
12 significance level of 5%. Within-group variations will be assessed by paired *t*-tests.
13
14
15 Missing values will be imputed by the last observation carried forward (LOCF) method.
16
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18 Safety data will be shown as frequencies and percentages by group and individual event.
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24 **PATIENT AND PUBLIC INVOLVEMENT**

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27 No formal patient advisory committee was established, and there was no patient or
28
29
30 public involvement in the design and planning of the study.
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35 **ETHICS AND DISSEMINATION**

36
37
38 This study will be conducted according to the protocol that has been prepared in
39
40
41 accordance with the Helsinki Declaration, Clinical Trials Act of the Japan Ministry of
42
43
44 Health, Labour and Welfare, and related laws and regulations. Each study patient will
45
46
47 be anonymously identified by a specific identification code and hence protected against
48
49
50 privacy invasion. The information and data of each patient will be used exclusively for
51
52
53 the study purpose and will never be disseminated outside the study.
54
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56 As a coordinating centre, SRD Co., Ltd. will share necessary information related to this
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6 study at the participating medical organizations in this study, conduct operations aimed
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8
9 at facilitating this study, and provide support to investigators. Data management and
10
11
12 monitoring are conducted by Juntendo Clinical Research and Trial Center, Juntendo
13
14
15 University Hospital. Details are specified in the Data Management Plan and Monitoring
16
17
18 Plan.

19
20
21 If a serious health hazard arises due to participation in this study, coverage benefits can
22
23
24 be received from insurance carried by a principal investigator, provided, however, that
25
26
27 compensation may be reduced or not compensated if it is proven that the health hazard
28
29
30 was caused by the research subject's own wilful act or gross negligence. In addition, if
31
32
33 there is no causal relationship between the newly occurring health hazard and the
34
35
36 deterioration of the originally affected disease, it is not covered by compensation. After
37
38
39 completion of the study by each research subject, the investigators will make efforts to
40
41
42 provide the best medical care obtained from the results of the research.

43
44
45 The results obtained from this study will be disseminated through an online study
46
47
48 registry (Japan Registry of Clinical Trials). The results will also be presented at relevant
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51 scientific conferences, such as a professional congress for movement disorders and
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54 Parkinson's disease, and in relevant medical journals.
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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

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6 decreased colonic motility, reflex inability of the pelvic floor muscles during attempted
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9 defecation, and IBS.[2,6] However, the precise mechanisms underlying constipation
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12 remain unknown. Thus, the same treatment algorithm used in patients with idiopathic
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15 chronic constipation should be recommended for constipation occurring in patients with
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18 PD.[2] Elobixibat is a highly potent selective IBAT inhibitor that results in excess bile
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21 acids in the colon, which is associated with increased water influx from the colon and
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23
24 colon motility via an interaction with TGR5.[15] These action mechanisms produce
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26
27 favourable effects on idiopathic chronic constipation and IBS.[17] Considering the
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29
30 effectiveness of macrogol and lubiprostone against PD-accompanying constipation,
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33 elobixibat is also expected to improve this condition. This study will provide the first
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36 evidence of whether elobixibat is a useful treatment for chronic constipation in patients
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38
39 with PD, as has already been demonstrated for idiopathic chronic constipation.
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45 We believe the randomised, clinical study proposed here will be useful for expanding
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48 treatment options for PD-related constipation in an evidence-based manner.
49

50
51 The study findings will be presented at relevant conferences and published in a
52
53
54 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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1
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6 study conduct. It should be noted that the two companies and their employees will never
7
8
9 be involved in any study procedures including collection, analysis or interpretation of
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12 data, ensuring (sub)investigators will be completely independent of the funders
13
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15 throughout study conduct.
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17 18 19 20 21 **Competing interests** 22

23
24 There are no competing interests.
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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

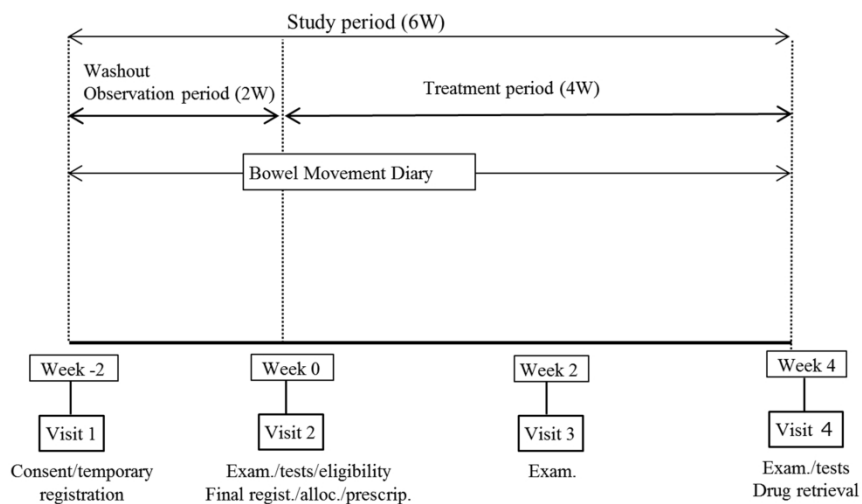


Figure 1 Study outline

254x190mm (307 x 307 DPI)

Figure 2

Visit	Observation period	Administration start	Treatment period	
	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)		
Patient background	○			
Subjective symptoms/objective findings		○	○	○
Physical examinations				
History/complications	○	○		
Physical examinations	○	○		○
Vital signs (blood pressure/pulse rate)		○		○
Use of investigational medication		←	→	→
Use of rescue/concomitant medication	←	←	←	←
Bowel Movement Diary	←	←	←	←
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)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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 ___

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1	Introduction			
2				
3	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__
4				
5				
6		6b	Explanation for choice of comparators	__NA__
7				
8	Objectives	7	Specific objectives or hypotheses	__6-8__
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial or single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__6-8, 10, 11__
11				
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	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__
17				
18				
19	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__
20				
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__10, 11__
23				
24				
25				
26		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__
27				
28				
29		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__13-15__
30				
31				
32		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__13-17__
33				
34	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__
35				
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40	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__
41				
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1	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
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	19-21
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

8				
9				
10	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
11				
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16	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
17				
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13-15
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-15
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13-15
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

32				
33	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
34				
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39		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
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1	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 ___
2				
3				
4				
5	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 ___
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ 8, 9, 10 ___
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 ___
11				
12				
13				
14	Methods: Monitoring			
15				
16	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 ___
17				
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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	___ 17,18 ___
23				
24				
25	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 ___
26				
27				
28	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 ___
29				
30				
31				
32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 22, 23 ___
35				
36				
37	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 ___
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	14
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
5				
6				
7	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
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	34, 35
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12				
13	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
14				
15				
16	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
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	26
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	34
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Material
32				
33				
34	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
35				
36				

*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.

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