PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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)
AUTHORS	Hatano, Taku; Oyama, Genko; Shimo, Yasushi; Ogaki, Kotaro; Nishikawa, Noriko; Fukae, Jiro; Nakamura, Ryota; Kurita, Naohide; Tsunemi, Taiji; Oji, Yutaka; Saiki, Shinji; Nishioka, Kenya; Takeshige, Haruka; Taniguchi, Daisuke; Ogawa, Takashi; Kamo, Hikaru; Eguchi, Hiroto; Fuse, Atsuhito; Nakajima, Asuka; Kano, Masayoshi; Nakajima, Sho; Yanagisawa, Naotake; Hattori, Nobutaka

VERSION 1 – REVIEW

REVIEWER	Santiago Pérez-Lloret University of Buenos Aires
REVIEW RETURNED	28-Jul-2021

GENERAL COMMENTS	This is a protocol for a clinical trial with elobixibat for constipation in patients with Parkinson's Disease. Overall, the protocol is scientifically sound. Notwithstanding, some aspects need further discussion: A more extensive revision of the action mechanism of elobixibat is needed. The authors should also discuss previous safety findings and discuss their implication for patients with Parkinson's Disease. The subgroup analysis that will be performed should be specified in details. Regarding the characteristics of patients, why were patients with irritable bowel syndrome not excluded? Furthermore, constipation may sometimes result from defecatory dysfunction due to pelvic floor dyssynergia. These patients respond poorly to laxatives. Why were they not excluded from the trial? There is no description on how the randomization list was generated. Use of Duodopa should be incorporated as an exclusion criteria. Regarding the sample size calculation, please provide information on the expected effect size and common standard deviation.

REVIEWER	Sylvia Dobbs King's College London
REVIEW RETURNED	02-Aug-2021

GENERAL COMMENTS	no 6. primary and secondary outcome very similar no 13. spirit checklist completed Since two hospital affiliated to same University hardly "a multi-centre trial". it is not clear what the status with respect to other laxatives is within the run in. Not explicit whether assessors are 'blind' Conclusions that can be drawn from this study are very limited. reviewed by Dr R John Dobbs DCH MD FRCP FBPhS and Dr Sylvia Dobbs MSc MD FRCP FBPhS Hon Consultant Physicians, The Maudsley and King's College Hospital Leads Host Microbiome Interaction: Clinical Pharmacology and Therapeutics Institute of Pharmaceutical Science, King's College London

VERSION 1 – AUTHOR RESPONSE

To the Comments of Reviewer 1

1. **A more extensive revision of the action mechanism of elobixibat is needed. The authors should also discuss previous safety findings and discuss their implication for patients with Parkinson's Disease.**
   As mentioned in the Introduction, elobixibat inhibits IBAT activity, leading to decreased reabsorption at the distal ileum and a subsequent elevated concentration of bile acids in the luminal side of the large intestine. The elevated bile acids interact with transmembrane G protein-coupled receptor molecules (TGR5), which induces water influx into the luminal side of the large intestine. The bile acid-TGR5 interaction also triggers the release of 5-HT (serotonin) into the intestinal wall, which activates intrinsic primary afferent neurons. This leads to an interneuron-mediated activation of motor neurons that finally activates large-intestinal motility.
   There is very little systemic absorption of elobixibat. We consider that the long-term safety of IBAT inhibition is not a serious concern, because a blockade of IBAT functionality by partial ileal bypass did not raise long-term safety issues[1,2]. A post-marketing study has also shown acceptable safety of elobixibat in patients with PD.

   [1] Buchwald H. Impact of cholesterol reduction on peripheral arterial disease in the Program on the Surgical Control of the Hyperlipidemias (POSCH), Surgery. 1996 Oct;120(4):672-9. doi: 10.1016/s0039-6060(96)80016-x.

   [2] Buchwald H. Overall mortality, incremental life expectancy, and cause of death at 25 years in the program on the surgical control of the hyperlipidemias, Ann Surg. 2010 Jun;251(6):1034-40. doi: 10.1097/SLA.0b013e3181deb4d0.

   The above information and related references have been added to the Introduction and Discussion sections of the revised manuscript. Specifically, 3 relevant articles are cited in the Introduction section (2 newly added references, #15 and #16, and the previous reference #29 now cited as #17). Following this change, all references were renumbered as required throughout the revised manuscript.

2. **The subgroup analysis that will be performed should be specified in details.**
   Subgroup analysis will be performed based on the presence or absence of complications, age (≥ or <65 years), Hoehn and Yahr scale (1 to 4), duration of the underlying disease (PD; ≥ or

<median), dose equivalence of L-Dopa prior to elobixibat initiation, and duration of chronic constipation (≥ or <20 years).

This information is now included in the 'Secondary endpoints' section of the revised manuscript.

3. **Regarding the characteristics of patients, why were patients with irritable bowel syndrome not excluded? Furthermore, constipation may sometimes result from defecatory dysfunction due to pelvic floor dyssynergia. These patients respond poorly to laxatives. Why were they not excluded from the trial?**
We referred to the Japanese guidelines for the treatment of chronic constipation, in which patients with irritable bowel syndrome (IBS) with constipation are included in the category of chronic constipation. It should be mentioned that IBS patients were included in previous clinical trials of elobixibat, in which the drug was shown in a post-hoc analysis to be have similar efficacy and safety profiles for IBS patients and other patient populations (Nakajima A, Taniguchi S, Kurosu S, Gillberg P-G, Mattsson JP, Camilleri M. Efficacy, long-term safety, and impact on quality of life of elobixibat in more severe constipation: Post hoc analyses of two phase 3 trials in Japan. Neurogastroenterol Motil. 2019;e13571. https://doi.org/10.1111/nmo.13571). In addition, IBS is known to be one of the prodromal gastrointestinal symptoms frequently observed in patients with PD (Liu B, Sjölander A, Pedersen NL, et al. Irritable bowel syndrome and Parkinson's disease risk: register-based studies. npj Parkinson's Dis 2021;7:5 DOI: https://doi.org/10.1038/s41531-020-00145-8). We did not exclude patients with IBS because it should be considered one of the gastrointestinal symptoms on the same basis as constipation in PD. This issue is now discussed in our revised manuscript (please see the 'Discussion and dissemination' section).
Patients with pelvic floor dyssynergia will be excluded from the study as stated in the exclusion criteria in 'Patient definitions' section as 'a PD patient will be excluded at temporary registration if he/she: has (or is suspected to have) organic constipation or dyschezia'.

4. **There is no description on how the randomization list was generated.**
A similar comment was provided by Reviewer 2 (please see comment No. 16 below).
As mentioned in the 'Study procedures and schedule' section, a specific ID number will be assigned to each patient judged eligible for study participation. Satt Co., Ltd. (Tokyo) will perform drug allocation and prepare a drug allocation table using IWRS. The study drugs will be sealed with specific drug numbers and delivered to the individual institutional sites according to the drug allocation table. At the final registration of patients via IWRS, the drug numbers (per drug and per patient) will be randomly allocated to the (sub)investigator. The key code of the allocation table will be opened by Satt after all study data are locked following the completion of the study.

This information is now included in the 'Study procedures and schedule' section.

5. **Use of Duodopa should be incorporated as an exclusion criteria.**
As described in the 'Rescue and concomitant medications/therapies' section, Duodopa is prohibited as a concomitant therapy. We therefore believe that patients receiving Duodopa therapy will be excluded in a practical sense. Even if Duodopa is used for a patient during the study, the use should be recorded in the patient's eCRF, which will lead to an exclusion of related data from analysis.

6. **Regarding the sample size calculation, please provide information on the expected effect size and common standard deviation.**
Based on the results from a domestic phase 2 study, the effect size was expected to be 3.06 (5.66 for elobixibat 10 mg vs. 2.60 for placebo) with a common standard deviation of 4.15.

This is now included in the 'Study population and statistical analysis' section.

To the Comments of Reviewer 2

7. Primary and secondary outcome very similar.

We will analyse endpoints (either primary or secondary) according to those defined in the study protocol. We agree with this comment because of the close relationship between the primary endpoint (weekly frequency of spontaneous bowel movements per each 7-day segment and Visit 4 vs. Visit 2 SBM frequency changes) and one of the secondary endpoints (weekly changes in SBM frequency). Please note that these endpoints are derived from those assessed in the phase 3 trial previously conducted (see Ref. below; please note that this article is cited as reference #17 in the revised version of the manuscript), though patient definitions were slightly different and less strict for the weekly frequency of bowel movements in the proposed study.
We would also like to point out that the other endpoints, such as stool form, use of rescue medications, questionnaire survey, and use of dopamine preparations, are defined as secondary endpoints only.

Ref. Nakajima A, Seki M, Taniguchi S, Ohta A, Gillberg P-G, Mattsson JP, Camilleri M. Safety and efficacy of elobixibat for chronic constipation: results from a randomised, double-blind, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial, Lancet Gastroenterol Hepatol. 2018 Aug;3(8):537-547.

8. SPIRIT checklist completed

We completed this form as defined in the study protocol.

9. Since two hospital affiliated to same University hardly "a multi-centre trial".

We apologize for the erroneous description in the 'Overall study design' section of our original manuscript. The original text stated that "This study is designed as a randomised, double-blind, placebo-controlled, parallel-group study at 2 academic centres (Juntendo University Urayasu Hospital, and Juntendo University Nerima Hospital), in which PD patients with chronic constipation will pre-prandially receive elobixibat ----". The "2 academic centres (Juntendo University Urayasu Hospital, and Juntendo University Nerima Hospital)" has now been corrected to "3 academic centres (Juntendo University Hospital, Juntendo University Urayasu Hospital, and Juntendo University Nerima Hospital)".
The medical institutions participating in the present study are indeed affiliated with Juntendo University, a Japanese government-approved school corporation.
However, please note that the three hospitals including the two pointed out by the reviewer and the newly added one (Juntendo University Hospital) as well as the fourth institution (Juntendo Clinical Research and Trial Center: see Title page) are all run and perform their activities independently.

Accordingly, we have revised the Overall study design section in the manuscript as "This study is designed as a multicentre, randomised, double-blind, placebo-controlled, parallel-group study at 3 academic centres (Juntendo University Hospital, Juntendo University Urayasu Hospital, and Juntendo University Nerima Hospital), in which PD patients with chronic constipation will pre-prandially receive elobixibat ------".

10. It is not clear what the status with respect to other laxatives is within the run in.

As stated in Rescue and concomitant medications/therapies section, laxatives including OTC drugs other than elobixibat will be prohibited throughout the study period including the observation (= run in) period and treatment period.

To clarify this, we inserted the phrase “throughout the entire study period” in the second paragraph of the same section. We also added the following sentence in the second paragraph: “The patient should self-report in his/her Bowel Movement Diary when any of the drugs/agents/therapies listed above are used.”

11. Not explicit whether assessors are 'blind'.

This comment is closely related to comment No. 9 from Reviewer 1 (please see above). As noted in our response to comment No. 9 and as mentioned in the ‘Study procedures and schedule’ section, a specific ID will be given to each patient judged eligible for study participation. Satt Co., Ltd. (Tokyo) will perform drug allocation and prepare a drug allocation table using IWRS. The study drugs will be sealed with specific drug numbers and delivered to the individual institutional sites according to the drug allocation table. At the final registration of patients via IWRS, the drug numbers (per drug and per patient) will be randomly allocated to the (sub)investigator. The key code of the allocation table will be opened by Satt after all study data are locked following the completion of the study.
The assessors and investigators will therefore be completely blinded to the study data until key code break.

This information is now included in the ‘Study procedures and schedule’ section.

12. Conclusions that can be drawn from this study are very limited.

The present study will firstly determine whether elobixibat is efficacious in improving chronic constipation which is a frequently observed symptom accompanying Parkinson’s disease. If the study results are positive, we will be able to expand therapeutic options and improve the quality of life of afflicted patients.