

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Long-term outcomes for Asian patients with X-linked hypophosphataemia: Rationale and design of the SUNFLOWER longitudinal, observational cohort study
AUTHORS	Kubota, Takuo; Fukumoto, Seiji; Cheong, Hae; Michigami, Toshimi; Namba, Noriyuki; Ito, Nobuaki; Tokunaga, Shin; Gibbs, Yoshimi; Ozono, Keiichi

VERSION 1 – REVIEW

REVIEWER	Rachel Crowley SVUH Ireland Site PI for BUR02 study of burosumab in XLH (Kiowa Kirin sponsor)
REVIEW RETURNED	28-Jan-2020

GENERAL COMMENTS	<p>The authors describe an observational study of XLH cases planned for Japan and Korea for which enrolment is on-going. The study aims to address the health, QoL and economic burden of XLH and the effect of treatment. As a general comment more detail should be provided in the protocol.</p> <p>Major comments</p> <ol style="list-style-type: none">1 - there is no mention of burosumab, including the abstract. The protocol should specifically state whether patients may receive this if licensed and marketed for the purpose (states clinical trial participation is an exclusion)2 - the published data in the burosumab trials could be used for calculation of sample size - this is a convenience sample but would be valuable to assess if powered to detect differences in outcomes detailed on p103 - exclusion criteria should be formally defined4 - laboratory assessments should be formally defined5 - complications of disease should be defined6 - QoL section suggest this may not be a comprehensive list of QoL assessment, suggest complete and state whether PROMIS approach validated in XLH7 - how will loss of working / learning opportunities be captured?8 - recruitment - please elaborate on age below which assent from next of kin is required, this is unusual for a European or American clinical study9 - the protocol should outline management of safety events10 - Kiowa Kirin's stakeholder status should be clear to the reader
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REVIEWER	Signe Sparre Beck-Nielsen Centre of Rare Diseases, Skejby Aarhus University Hospital
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	Denmark Provides consultancy for Kyowa Kirin, and has received a research grant from Kyowa Kirin.
REVIEW RETURNED	11-Feb-2020

GENERAL COMMENTS	<p>Review BMJ Open, Febr. 2020</p> <p>"Long-term outcomes for Asian patients with X-linked hypophosphataemia: Rationale and design of the SUNFLOWER longitudinal, observational cohort study"</p> <p>The authors present a manuscript/protocol reporting an interesting and warranted study investigating long-term outcomes for Asian patients with XLH. The manuscript is well written</p> <p>The authors may consider to presenting the aims of the study within the same section of the protocol, they appear at different sections.</p> <p>Suggestions for the protocol:</p> <p>INTRODUCTION:</p> <p>p. 6, line 48: Please address that dental problems indeed are also an issue in children with XLH.</p> <p>p. 6: Awareness of childhood complications as craniosynostosis and Chiari I malformations in both children and adults should be added.</p> <p>p. 8, lines 36-37: The aim 'to shed new light on the patients who have milder clinical manifestations' is not likely to be met as these patients with milder clinical manifestations are usually not followed at the outpatient clinic.</p> <p>METHODS AND ANALYSIS:</p> <p>p. 9, line 34: Please clarify that both adults and children with XLH will be included. The sentence as it is may lead falsely to the understanding that children only are included.</p> <p>p. 10, line 20: Please clarify how you define a previous history or physical sign of osteomalacia?</p> <p>p. 10, lines 25-31: Please specify the exclusion criteria 'based on patient safety and burden'. It is unclear how participation in a</p>
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	<p>longitudinal observational cohort study may have an impact on patient safety and burden?</p> <p>p. 11, line 3: Provide a clear definition to distinguish between a fracture caused by trauma and a pseudofracture appearing at skeletal sites with stress and decreased repair. Data should be reported as traumatic fractures (if possible specify low or relevant trauma) or pseudofractures.</p> <p>p. 11, line 3: Data on nephrocalcinosis and renal function is advised to be captured in children also, where available.</p> <p>In addition, data on parathyroid hormone levels/ALP/Urine Ca/cr etc. should be captured. A complete list of biochemistry being captured is desirable.</p> <p>p. 11, line 35: aBMD z-scores are of limited value in XLH as they are severely confounded by wider bones. DXA may be useful if the patient is his or her own control. Please specify which BMD measurements you will capture.</p>
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VERSION 1 – AUTHOR RESPONSE

Responses to the comments of Reviewer #1

The authors describe an observational study of XLH cases planned for Japan and Korea for which enrolment is on-going. The study aims to address the health, QoL and economic burden of XLH and the effect of treatment. As a general comment more detail should be provided in the protocol.

1. there is no mention of burosumab, including the abstract. The protocol should specifically state whether patients may receive this if licensed and marketed for the purpose (states clinical trial participation is an exclusion)

Response: *As suggested, we have added information on patients who receive treatment with burosumab in the Methods and Analysis section (under Data collection, pages 11–12) and modified Table 1 (pages 26–27) accordingly. We also mentioned the use of burosumab in the abstract (pages 3–4).*

2. the published data in the burosumab trials could be used for calculation of sample size - this is a convenience sample but would be valuable to assess if powered to detect differences in outcomes detailed on p10

Response: *We thank the Reviewer for the suggestion. However, at the time of study planning, clinical trial information that could be referred to for calculating the sample size was not yet available. Therefore, the sample size for this study was based on feasibility and the number of potential XLH outpatients who can be enrolled in participating medical institutions, which was found to be 100 cases in Japan and 60 cases in Korea (page 9).*

3. exclusion criteria should be formally defined

Response: We appreciate the suggestion. However, there are no exclusion criteria other than those which we have already described in the manuscript, and we revised the inclusion and exclusion criteria sections to be clearer (page 10). Patients with diseases other than those specified in the inclusion criteria will not be included in this study.

4. laboratory assessments should be formally defined

Response: As suggested, we added a new section in the Methods and Analysis section to describe laboratory assessments (page 13).

5. complications of disease should be defined

Response: We have added a new section in the Methods and Analysis section to describe disease-related and treatment-related complications (page 13).

6. QoL section suggest this may not be a comprehensive list of QoL assessment, suggest complete and state whether PROMIS approach validated in XLH

Response: We thank the Reviewer for the suggestion. QoL will be assessed using the questionnaires listed in the QOL assessment section of the manuscript (pages 14–15). Currently, no published information has confirmed the validity of the PRO measurement for evaluating QOL in XLH patients. The rationale for the use of this assessment method was based on the fact that it was used in a previous study of children with XLH (Imel EA et al. Lancet 2019;393:2416–27).

7. how will loss of working / learning opportunities be captured?

Response: Patient-reported outcome data concerning working/learning will be collected annually for patients aged <18 years and every 2 years for patients aged ≥18 years, and a specifically prepared assessment sheet will be used for patients who are elementary school-aged children or older. We have added this explanation in the Methods and Analysis section (under QOL assessment, page 15).

8. recruitment - please elaborate on age below which assent from next of kin is required, this is unusual for a European or American clinical study

Response: The age for which approval from a parent/guardian is required, as informed consent for participation in a research study, is <20 years in Japan and <19 years in Korea. This was already mentioned in the Method and Analysis section (under Target population and sample size, page 9).

Assent (defined as active agreement by a minor, not qualified to give consent, to participate in a research study) was obtained using an informed assent document for patients aged <16 years at the time of enrollment.

The following table provides a more detailed explanation of the age groups and the requirement for assent and/or informed consent from the patient and/or parent/legal guardian.

Age at informed consent	Assent form	Informed consent form	
	Patient	Parent/legal guardian	Patient
<10 years	○ (for early elementary school children)	○	—
10–12 years	○ (for higher-grade elementary school children)	○	—
13–15 years	○ (for junior high school students)	○	—
16–19 years	—	○	○
≥20 years	—	—	○

The requirement for assent/consent in our study was based on the following references:

1. ICH-E11 Guideline: Clinical investigation of medicinal products in the pediatric population (in Japanese; Notification No. 1334 from Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated December 15, 2000). Available at: <https://www.pmda.go.jp/files/000156072.pdf>
2. Committee on Bioethics, American Academy of Pediatrics: Informed consent, parental permission, and assent in pediatric practice. *Pediatrics* 1995;**95**:314–7.
3. Q & A for ICH-E11 Guideline: Clinical investigation of medicinal products in the pediatric population (in Japanese, dated June 22, 2001). Available at: <https://www.pmda.go.jp/files/000156578.pdf>
4. Ethical guidelines for medical and health research involving human subjects (Announcement No. 3 from the Ministry of Health, Labour and Welfare/Ministry of Education, Culture, Sports, Science and Technology in Japanese, dated December 22, 2014) Available at: <https://www.mhlw.go.jp/file/06-Seisakujouhou-12600000-Seisakutoukatsukan/0000168764.pdf> [in Japanese], <https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf> [provisional English translation]
5. Civil Act; Act No. 13125, Partial Amendment (February 3, 2015), enforced on February 4, 2016. Available at: <http://www.law.go.kr/LSW/eng/engLsSc.do?menuId=2§ion=lawNm&query=%EB%AF%BC%EB%B2%95&x=0&y=0#liBgcolor1>

9. the protocol should outline management of safety events

Response: We thank the Reviewer for the suggestion. Indeed, data on adverse events will be collected. However, as this is an observational study, management of safety events will not be performed. Adverse events will be managed by the treating physician according to their judgement. In addition to evaluating adverse events, safety in terms of renal function will be evaluated by serum and urine analysis and renal ultrasonography. We have clarified this in the Methods and Analysis section (under Assessments, page 12).

10. Kiowa Kirin's stakeholder status should be clear to the reader

Response: As suggested, we have clarified this in the Funding section (page 16).

Responses to the comments of Reviewer #2

The authors present a manuscript/protocol reporting an interesting and warranted study investigating long-term outcomes for Asian patients with XLH. The manuscript is well written. The authors may consider to presenting the aims of the study within the same section of the protocol, they appear at different sections.

Suggestions for the protocol:

INTRODUCTION:

1. p. 6, line 48: Please address that dental problems indeed are also an issue in children with XLH.

Response: As suggested, we have added a sentence regarding dental problems in the Introduction section (page 6).

2. p. 6: Awareness of childhood complications as craniosynostosis and Chiari I malformations in both children and adults should be added.

Response: Thank you for the suggestion. We have added a sentence about disease-related complications with supporting citations in the Introduction section (pages 6–7).

3. p. 8, lines 36-37: The aim ‘to shed new light on the patients who have milder clinical manifestations’ is not likely to be met as these patients with milder clinical manifestations are usually not followed at the outpatient clinic.

Response: In this study, patients will be registered regardless of disease severity. We agree that it may be challenging to recruit patients with milder clinical symptoms. However, once identified during a visit to a medical institution, or through analysis of the medical history of a patient’s family member or a relative during a visit, even if the number of such cases is small, these patients can be followed up in an outpatient setting.

METHODS AND ANALYSIS:

4. p. 9, line 34: Please clarify that both adults and children with XLH will be included. The sentence as it is may lead falsely to the understanding that children only are included.

Response: As suggested, we have clarified in the Methods and Analysis section (under Target population and sample size, page 9) that both adults and children were included in the study.

5. p. 10, line 20: Please clarify how you define a previous history or physical sign of osteomalacia?

Response: The retrospective data will be used to determine a previous history of osteomalacia based on the definition of osteomalacia stated in the Diagnosis Manual of Rickets and Osteomalacia by The

Japanese Society of Bone and Mineral Research. We have clarified this in the Methods and Analysis section (under Inclusion criteria, page 10).

6. lines 25-31: Please specify the exclusion criteria 'based on patient safety and burden'. It is unclear how participation in a longitudinal observational cohort study may have an impact on patient safety and burden?

Response: We apologize for the confusing text. We have deleted the related text in the Methods and Analysis section (under Exclusion criteria, page 10) to avoid further confusion.

7. p. 11, line 3: Provide a clear definition to distinguish between a fracture caused by trauma and a pseudofracture appearing at skeletal sites with stress and decreased repair. Data should be reported as traumatic fractures (if possible specify low or relevant trauma) or pseudofractures.

Response: In this study, to adequately evaluate a pseudofracture, the participating institution will be requested to provide imaging data, such as radiographs, computed tomography images, and magnetic resonance images, and the registered data will be evaluated by the Central Evaluation Committee consisting of orthopedic surgeons and radiologists. If a study patient presents a fracture, the attending physician will fill out an evaluation form in which the fracture will be classified as traumatic or non-traumatic. We have added these details to the Methods and Analysis section (under Outcomes, page 11).

8. p. 11, line 3: Data on nephrocalcinosis and renal function is advised to be captured in children also, where available. In addition, data on parathyroid hormone levels/ALP/Urine Ca/cr etc. should be captured. A complete list of biochemistry being captured is desirable.

Response: We have clarified that safety in terms of renal function will be evaluated by serum and urine analysis and renal ultrasonography in the Methods and Analysis section (under Assessments, page 12). Additionally, we added a new subsection in the Methods and Analysis section to describe laboratory assessments.

9. p. 11, line 35: aBMD z-scores are of limited value in XLH as they are severely confounded by wider bones. DXA may be useful if the patient is his or her own control. Please specify which BMD measurements you will capture.

Response: For patients aged ≥ 18 years, bone mineral density will be measured by dual-energy X-ray absorptiometry at the hip, lumbar spine, or other sites. We have clarified this in the Methods and Analysis section (under Data collection, page 12).

VERSION 2 – REVIEW

REVIEWER	R Crowley SVUH Ireland
REVIEW RETURNED	19-Mar-2020
GENERAL COMMENTS	No further comments

REVIEWER	Signe Sparre Beck-Nielsen Centre for Rare Diseases, Aarhus University Hospital, Denmark Provides consultancy to Kyowa Kirin
REVIEW RETURNED	06-Apr-2020

GENERAL COMMENTS	<p>In general, the manuscript has improved after the revision. The conflicting statement of the aim of this study, and its limitations stating that including XLH patients with milder disease will be less likely, is unfortunately not sufficiently addressed. Also, there is a need for a further clarification of how the data captured will allow drawing the warranted conclusions stated in the aim of the study.</p> <p>p. 6: Consider changing the sentence 'Children with XLH often present with dental problems...' to 'Children with XLH often develop dental problems...' as dental abscesses are usually not the presenting symptom.</p> <p>p. 8: There is an unaddressed concern of how this study design will be able to provide the necessary data to investigate the aim stated by the authors; 'This study should expand the foundations of our knowledge by shedding new light on the patients who have milder clinical manifestations. This, in turn, will ultimately provide us with much-needed basic information to assess which patients require treatment, when the treatment should be provided, and what medication is most appropriate'.</p> <p>Please explain further the contrary statement of the aim (p. 8) of including XLH patients with milder clinical manifestations and your limitations stated (p. 4): '...it will not be possible to examine the disease process in untreated patients.' and 'Undiagnosed patients with fewer or less severe clinical manifestations may be unaware of their XLH status; thus, cases with a mild disease phenotype may be poorly represented in the analysis, potentially resulting in a bias towards more severe forms of the disease.'</p> <p>Please explain further how the authors have considered using the data captured retrospectively and from up to 5 years of follow-up to allow conclusions concerning: 'how to assess which patients require treatment, when the treatment should be provided, and what medication is most appropriate.'</p>
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VERSION 2 – AUTHOR RESPONSE

Responses to the comments of Reviewer #2

In general, the manuscript has improved after the revision.

1. The conflicting statement of the aim of this study, and its limitations stating that including XLH patients with milder disease will be less likely, is unfortunately not sufficiently addressed. Also, there is a need for a further clarification of how the data captured will allow drawing the warranted conclusions stated in the aim of the study.

Response: Please see below for the detailed responses to each of your specified points. We believe that we have now removed the perceived conflict between the study aims and limitations, and have clearly stated our aspirations for how the study data will be used to inform and underpin future clinical decision making.

2. p. 6: Consider changing the sentence 'Children with XLH often present with dental problems...' to 'Children with XLH often develop dental problems...' as dental abscesses are usually not the presenting symptom.

Response: We have revised the sentence as requested.

3. p. 8: There is an unaddressed concern of how this study design will be able to provide the necessary data to investigate the aim stated by the authors; 'This study should expand the foundations of our knowledge by shedding new light on the patients who have milder clinical manifestations. This, in turn, will ultimately provide us with much-needed basic information to assess which patients require treatment, when the treatment should be provided, and what medication is most appropriate'.

Response: As noted, on page 8 we state that the study aim is to better understand XLH. Thus, the study is designed to enroll all eligible XLH patients, regardless of disease severity (as stated in the Methods, page 9), which should ensure that we are able to observe the clinical course in a wide range of patients displaying different symptoms or differing symptom severity. The specific text on page 8 (last paragraph of the Introduction) regarding mild disease has been deleted, as it is not the primary aim of this analysis, but was intended to be an aspirational future goal once a greater quantity of data are available. We have also slightly revised the text on page 9 (1st paragraph of 'Target population and sample size' section) to confirm that we are actively recruiting patients of all disease severities, from mild through to severe.

4. Please explain further the contrary statement of the aim (p. 8) of including XLH patients with milder clinical manifestations and your limitations stated (p. 4):

'...it will not be possible to examine the disease process in untreated patients.'

and

'Undiagnosed patients with fewer or less severe clinical manifestations may be unaware of their XLH status; thus, cases with a mild disease phenotype may be poorly represented in the analysis, potentially resulting in a bias towards more severe forms of the disease.'

Response: We have changed the wording of our statement on page 4 ('Strengths and limitations of this study' section) regarding untreated patients. Since the study protocol does not exclude untreated patients, such patients may be enrolled. However, as we anticipate that most patients are likely to have received some form of treatment, we have suggested that any analysis of the disease course in untreated patients is likely to be limited by the availability of data.

As noted in our response to comment #3, we have revised the sentence on page 8 (last paragraph of the Introduction) to clarify the study aim that we are endeavoring to collect data on all patients with XLH, regardless of disease severity. We consider that it may be challenging to recruit patients with milder clinical symptoms and this remains as a possible study limitation on page 4, although we have revised the wording slightly to reiterate that patients of all severities are eligible for enrolment. Nonetheless, once identified during a visit to a medical institution, or through analysis of the medical history and family tree of an afflicted relative, even if the number of such patients is small, these mild cases can be followed up in an outpatient setting. Until enrolment and data collection are complete, we are unable to say how much information regarding mild disease we will be able to obtain from the current study, and how many questions will remain unanswered and awaiting elucidation from future analyses.

5. Please explain further how the authors have considered using the data captured retrospectively and from up to 5 years of follow-up to allow conclusions concerning: 'how to assess which patients require treatment, when the treatment should be provided, and what medication is most appropriate.'

Response: Assessing which patients need treatment, when to give treatment, and what drugs are most appropriate will be future research questions that will be considered using the data set obtained in this study. We have revised the last paragraph of the Introduction (page 8) to clarify how data accrued in this study will contribute to future research.

We have stated that this study is an observational study aimed at collecting the data necessary to evaluate the characteristics, disease course, physical, mental, and financial burden of XLH, and the efficacy and safety of treatment for up to five years. At the current point in time, information of this range and depth is lacking, making it hard for clinicians to know when to initiate treatment, the types of treatments that could or should be initiated, and what the outcomes might potentially be. The study aims to fill this knowledge gap by collecting data on various types of treatment in patients across a range of ages and disease severities. We believe the data collected will provide useful information and help clinicians make decisions towards better management of XLH.