National Institute for Health and Care Excellence

Single Technology Appraisal

Burosumab for treating X-linked hypophosphataemia in adults [ID3822]

Response to consultee and commentator comments on the draft remit and draft scope

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Kyowa Kirin (company)	Yes, Kyowa Kirin considers the appraisal of burosumab for treating X-linked hypophosphataemia (XLH) in adults to be appropriate and should be through the Highly Specialised Technologies (HST) appraisal route and not the Single Technology Appraisal (STA) route. An approved treatment option in XLH for adults is long awaited for people living with this very rare condition and their respective families. Adults with XLH experience a significant burden, living with a disease that is lifelong, progressive and debilitating (1). With no therapeutic options currently available, there is a high unmet need for an effective treatment to address the biological pathology of XLH. Burosumab (Crysvita ®) is the first and only treatment for XLH which addresses the pathophysiology of the disease (FGF23-induced hypophosphataemia). It has been shown to modify the life course of the disease, substantially improve XLH burdensome symptoms which include pain, stiffness and fatigue that impact physical functioning as well as positively effect fractures.	Comments noted. After considering information received from consultation and comments from the scoping workshop it was agreed that the appropriate route for burosumab was as a single technology appraisal.

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		Kyowa Kirin considers that the appraisal of burosumab for the treatment of XLH in adults meets all the criteria for appraisal through the HST programme. Detailed comments on this issue including number of patients and treatment centres are outlined below under the Section "**Questions for consultation**".	
	Brittle Bone Society	YES	Comment noted.
	Metabolic Support UK	It is timely and appropriate for this topic to be referred to NICE given that currently no alternative treatments are available. We have concerns about the intention to refer this for an STA rather than to the HST programme which has previously considered Burosumab for XLH.	Comment noted.
	Genetic Alliance	We note our member organisation XLH UK's submission provides evidence that the prevalence of XLH in the adult population is estimated to be 1 in 90,000. ONS data from 2019 estimated a population of 54 million adults in the UK. Applying this prevalence would indicate approximately 600 adults in the UK (approximately 500 in England) would be affected by XLH. This population level and prevalence gives us concern that this treatment might be more appropriately examined using the HST pathway instead of the STA pathway proposed. The childhood indication was appraised through the HST route. As XLH is a rare condition, and suffers from the usual challenges in demonstrating the value of a rare disease medicine, such as small and relative short term clinical trials, difficulties collecting quality of life data, etc. The technology appraisal programme is currently less well suited for rare disease medicines such as this with small population sizes, relatively immature evidence bases, potential for lifelong use and impacts beyond direct health benefits. The HST programme was developed as a pathway to	Thank you for your comment. Following the scoping workshop, the population in the background section has been updated.

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		assess technologies for both rare and very rare conditions, and would be the most appropriate route for evaluation of Burosumab. It is certainly the case the Burosumab is an appropriate treatment for NICE to assess whether using HST or STA processes.	
	XLH UK	This topic is both timely and highly appropriate for NICE consideration given that no alternative treatments are available to adults with XLH. There is a discrepancy in prevalence that you have. The latest evidence suggests that there are 1 in 90,000 adults living with XLH in England. **Prevalence and Mortality of Individuals With X-Linked Hypophosphatemia: A United Kingdom Real-World Data Analysis** https://academic.oup.com/jcem/article/105/3/e871/5626435	Thank you for your comment. Following the scoping workshop, the population in the background section has been updated.
	NHS England	Yes. It is appropriate to refer this topic to NICE for appraisal	Comment noted.
	Metabolic Bone Centre, Sheffield Teaching Hospitals NHS FT	Yes- this assessment is needed however, we are questioning why isn't the highly specialised technique guidance used as per children approval?	Thank you for your comment. No action required.
	Royal National Orthopaedic Hospital NHS Trust	It is appropriate for this topic to be reviewed by NICE. Burosumab is currently available for treatment of X-linked hypophosphataemia in children and young people (Highly specialised technologies guidance [HST8]). It is important to have guidance approved for adults so that care is appropriately managed as young people transition to adult services.	Comment noted.

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	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	Treatment of XLH in adults has problems which are not encountered in paediatric practice. These are notably related to the long-term complications such as enthesopathy and nerve compression. In addition, there are long term complications of treatment such as hyperparathyroidism with its consequences for bone and renal tract. It is likely that burosumab will offer a step change in treatment for such patients. In addition, there are some areas of XLH management in adults which are not readily amenable to current medical therapy and may only be amenable to surgical treatment. Some of these, such as insufficiency fractures, would be predicted to respond to burosumab. Many adult patients have children in their families who are already receiving burosumab and fail to understand why they do not have ready access to the treatment. Now that marketing authorisation is being sought for this agent in adults with XLH it would appear entirely appropriate that NICE appraise the use of this treatment at this time.	Thank you for your comment. No action required.
	University Hospitals Bristol and Weston NHS Foundation Trust	Absolutely. There is a clinical need for a sub-group of adult patients with XLH and I have seen first-hand the positive impact that burosumab can make in an adult setting. One patient described the treatment as 'life-changing'.	Thank you for your comment. No action required.
Wording	Kyowa Kirin (company)	Kyowa Kirin believes that the remit as written "To appraise the clinical and cost effectiveness of burosumab within its marketing authorisation for treating X-linked hypophosphataemia (XLH) in adults" is appropriate	Comment noted.
	Brittle Bone Society	YES	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
	Metabolic Support UK	The wording is appropriate	Comment noted
	XLH UK	Recommendation to add “rare” where it reads: X-linked hypophosphataemia (XLH) is a rare genetic disorder characterised by low levels of phosphate in the blood. We do not believe that the one and only sentence on adult manifestations accurately describes the breadth or disabling extent of the complications associated to having XLH in adulthood. In adults, the main manifestations of XLH include chronic bone pain, slow healing fractures, joint stiffness and restricted movement of the spine and hips, causing a profound socioeconomic and comorbidity impact. Neurological, hearing and, in severe cases, spinal cord compression complications. Many adults will eventually develop hyperparathyroidism and or nephrocalcinosis as a result of phosphate and active vitamin-D therapy. Many adults also experience early onset (starting in their early thirties), progressive and debilitating calcification of the soft tissue (enthesopathy) in weight bearing joints from ankles to knees to hips and spine. Children have often required multiple corrective surgeries to correct deformities or unresolved fractures of the femurs, tibias, fibulas, with external and internal fixation. Then later in life patients who did not have early corrective surgery may require it in young adulthood. Others who did have surgery earlier may need to correct the earlier surgeries. In both children and adults the surgeries often require longer than standard healing and recovery times due to poorly mineralised bones. Adults with XLH may also find that joint replacements may be required significantly earlier than expected when	Comment noted. The background section has been updated to include hearing loss.

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		compared with the general population, with XLH patients requiring knee and hip replacements as early as their thirties.	
	NHS England	Yes. The wording of the remit reflects the issues of clinical and cost effectiveness about the technology that NICE should consider	Comment noted
	Metabolic Bone Centre, Sheffield Teaching Hospitals NHS FT	Yes	Comment noted
	Royal National Orthopaedic Hospital NHS Trust	The remit is appropriate.	Comment noted
	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	It is sufficiently wide ranging to capture all relevant issues	Comment noted

Section	Consultee/ Commentator	Comments [sic]	Action
Timing Issues	Kyowa Kirin (company)	Not applicable	Comment noted
	Brittle Bone Society	Urgent for the people currently with XLH and who believe the treatment will aid their suffering.	Comment noted
	Genetic Alliance	XLH is a progressive and irreversible condition, and there is no currently available treatment that addresses the fundamental action of the condition in the way that Burosumab does. Any adult who may in future access the treatment will benefit from access as soon as possible. As with any progressive and irreversible condition, every day without a treatment means the condition progresses further. A timely evaluation would therefore be of benefit to adults living with XLH.	Comment noted
	NHS England	The relative urgency is routine.	Comment noted
	Metabolic Bone Centre, Sheffield Teaching Hospitals NHS FT	Soon – patients are receiving treatment through early access and clinical trials, and there needs to be guidance in place when these routes end.	Comment noted
	Royal National Orthopaedic Hospital NHS Trust	The treatment is already approved for use in children and young people. Without an appraisal in adults, there is a risk that patients may fall into a “treatment gap” once they reach 18 years. It is therefore important that the proposed appraisal happens in a timely manner.	Thank you for your comment. No action required.

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	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	As noted above the timing is appropriate. Patients with XLH are currently suffering a significant degree of morbidity associated with unaddressed health care needs and so whilst not life saving or extending any delay would be associated with significant unnecessary suffering.	Thank you for your comment. No action required.
Additional comments on the draft remit	Kyowa Kirin (company)	As mentioned above, the scope for this appraisal meets all seven HST criteria	Comments noted. After considering information received from consultation and comments from the scoping workshop it was agreed that the appropriate route for burosumab was as a single technology appraisal.
	Metabolic Bone Centre, Sheffield Teaching Hospitals NHS FT	A highly specialised assessment would be a more appropriate route for this treatment.	Comments noted. After considering information received from consultation and comments from the scoping workshop it was agreed that the appropriate route for burosumab was as a

Section	Consultee/ Commentator	Comments [sic]	Action
			single technology appraisal.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Kyowa Kirin (company)	We suggest the wording is updated to provide further information, particularly with regard to the impact of the disease on adults, as follows: "X linked hypophosphataemia (XLH) is a rare genetic, progressive and lifelong disorder characterised by chronic low levels of phosphate in the blood (hypophosphataemia) due to excess of a regulating factor known as fibroblast growth factor 23 (FGF23). Phosphate plays an essential role in human cellular processes as well as in tissue structure and function throughout life. Clinical manifestations of XLH usually begin in early childhood including rickets and weakened skeletal bones that result in lower limb deformities, stunted growth and dental abscesses. With the fusion of the growth plates, the skeletal deformities become permanent. The presence of these deformities, in combination with the ongoing exposure to chronic hypophosphataemia, leads to the development of further debilitating morbidities that have a deleterious impact on multiple body systems throughout adult life, including fractures, pseudofractures, osteoarthritis, enthesopathies, hearing problems as well as ongoing serious dental problems (2). Most adults experience high levels of bone and joint pain, stiffness and fatigue that have a significant impact on their mobility and their ability to perform daily activities, and limit their social, family and work life. These combined issues affect their mental health profoundly (3). Furthermore, the inherited nature of XLH means that different generations of the same family often live with the condition. This increases the impact on	Thank you for your comment. Following the scoping workshop, the population listed in the background has been updated and mental health impact has been added.

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		patients and their carers, both in terms of health, lost earnings and social isolation. More recently, Crysvita® (burosumab) has become available for children and young people with XLH (NICE HST8). For adults, without the availability of burosumab, there are no treatments to address the pathophysiology of XLH. Current treatment options include oral phosphate and active vitamin D analogues but these do not address low serum phosphate levels in XLH, are burdensome and have an associated risk of complications due to frequent inconvenient dosing regimens over a daily period." Kyowa Kirin also notes that the epidemiological estimate of adult cases with XLH in England is wrong and needs to be corrected based on the recent UK epidemiological study (Hawley et al, 2020) (4) presented in details under Section ""**Questions for consultation**". The text in the background section needs to be amended as follows: "It is estimated that, in total, there are between 291 and 578 adults with XLH in England".	
	Brittle Bone Society	We primarily support the OI community, however we are aware of many aspects around similar challenges in the XLH area of health. XLH is not our area of expertise. Our community share the same group of highly skilled expert healthcare professionals.	Thank you for your comment. No action required.
	Metabolic Support UK	The symptoms included in the background is not comprehensive of all the symptoms, signs and the resulting complications of XLH; i.e. muscle weakness, hearing impairment and effects on other organs. We recognise that neurological manifestations are mentioned but want to see a full and more inclusive list. Osteaomalacia causes a range of symptoms we would expect to see described and explored in full in the final scoping document. This would better reflect the impact of XLH on:	Thank you for your comment. Following the scoping workshop, the population listed in the background has been updated and mental health impact has been added.

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		• Mental health: as it is severely impacted by living with this degenerative Bone condition. Depression and anxiety impact heavily on patients, family, offspring, partners and carers. Supportive treatment including clinical psychology and pain management is rarely considered. • Employability and ability to work is severely affected by the debilitating nature of disease and the surgeries that are more often required than not. The population estimates do not resonate with our understanding of prevalence and incidence of XLH in the UK and request that there is further review of current literature and expert opinion.. The systematic review study referenced to in the scoping document is dated back to 2005. The following developments in the XLH UK community since then might allow for more accurate incidence and prevalence figures to be generated: • More research has been completed, and published, since 2005 giving us a clearer picture of the disease. • There is more awareness of XLH among clinicians and the patient community leading to what we hope is more accurate and timely diagnosis. This view is based on what we have seen first-hand as a charity. • A new charity (XLH UK) was registered to provide first line support alongside MSUK.	
	Genetic Alliance	We note and support the comments from our member XLH UK which expand upon the breadth of impact of the condition. The 52 words in the background information which describe the impact of the condition cover a multitude of individual physiological symptoms, which each have consequences for future health, life-style and opportunity, and which in some cases have consequences for psychological symptoms. While we appreciate that these documents cannot be comprehensive, we believe the condition in adults could be valuably described in greater detail.	Thank you for your comment. Following the scoping workshop, the population listed in the background has been updated and mental health impact has been added.

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		As discussed in a previous answer, XLH UK have shared evidence in their submission that would indicate the population of adults in the England with the condition is around 500.	
	XLH UK	There are other complications that have not been stated in the Draft Scope, Appendix B, associated to adults with XLH: these include hearing loss, tooth loss, dental abnormalities, muscle weakness, fatigue, short stature and the severity and debilitating effects of the enthesopathy and arthritis on the major joints. Resulting bone pain, fractures without trauma and mobility restrictions are the main causes of adult patients not being able to continue with employment and or chores and social interactions. Consequently, chronic depression and comorbidities are highly likely among the XLH population in England. Reliance on long term pain medication, and in some opioid medicines. Those in relationships may find it difficult to plan for a family when they are aware of the x-linked dominant pattern of inheritance and those with family where children and great grandchildren have inherited XLH can equally have a psychological strain and carry additional socioeconomic burdens on the family.	Thank you for your comment. Following the scoping workshop, the population listed in the background has been updated, and hearing loss and mental health impact have been added.
	NHS England	Yes. The background information is accurate and complete.	Comment noted.
	Metabolic Bone Centre, Sheffield Teaching Hospitals NHS FT	Yes, could add information on comparators, see comment below. The estimated number of adult XLH patients in the UK is consistent with number seen locally	Comment Noted.

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	Royal National Orthopaedic Hospital NHS Trust	The description of the condition is accurate. Dental disease is also seen commonly in the adult population. Prevalence figures appear accurate based on published data. The majority of adults will have been diagnosed during childhood, although some may not be under regular follow-up. Douglas C, et al. Outcome of adult patients with X-linked hypophosphatemia caused by PHEX gene mutations. J Inherit Metab Dis. 2018; 41(5): 865–876. Samuel H, et al. Higher prevalence of non-skeletal comorbidity related to X-linked hypophosphataemia: a UK parallel cohort study using CPRD. Rheumatology (Oxford) 2020 (online ahead of print) Hawley S, et al.Prevalence and Mortality of Individuals With X-Linked Hypophosphatemia: A United Kingdom Real-World Data Analysis. J Clin Endocrinol Metab. 2020;105(3):e871-8	Thank you for your comment. No action required.
	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	The initial paragraph is a little over simplistic and fails to capture the complexity of the underlying condition: • FGF23 is not normally considered to be a “hormone” but a signalling peptide • The raised levels of FGF23 are believed to lead to the increased bone formation which characterises much of the clinical burden in adults with this condition The paragraph appears to be written from a paediatric perspective with an undue emphasis on childhood presentation and manifestations with	Thank you for your comment. “Hormone” in the background has been changed to “signalling peptide”

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		concomitant lack of emphasis on the adult manifestations which are given scant consideration. Moreover, there is an implication that almost all cases seen in adults have been diagnosed in childhood. This is emphatically not the case: a significant minority, perhaps up to 20% of patients seen in adult clinics have not been diagnosed previously.	
The technology/ intervention	Kyowa Kirin (company)	The draft scope states that burosumab does not have market authorisation in adults. This is incorrect and should be amended. On 30th September 2020, the European Medicines Agency (EMA) approved burosumab for the treatment of XLH in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults. (5)	Comment noted. Scope has been updated to reflect that the marketing authorisation has been updated to approve use for adults.
	Brittle Bone Society	Unfortunately this is not an area of expertise we are confidently qualified in, to be able to comment	Comment noted.
	Metabolic Support UK	This section is accurate to the best of our knowledge.	Comment noted.
	NHS England	Yes. The description of the technology is accurate.	Comment noted.
	Metabolic Bone Centre, Sheffield Teaching Hospitals NHS FT	Yes, could add information on effect on healing pseudofractures	Comment noted.

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	Royal National Orthopaedic Hospital NHS Trust	It should be stated that KRN23 is administered by monthly injection in adults	Comment noted.
	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	Yes	Comment noted.
Population	Kyowa Kirin (company)	The description of the target population for burosumab should be amended as follows: “Adults with a confirmed diagnosis of XLH who have evidence of progressive disease due to chronic hypophosphataemia and are experiencing persistent and debilitating symptoms despite prior treatment with conventional therapy”. This reflects the population that will receive treatment with burosumab. It also corresponds to the criteria[1] of burosumab’s Patient Early Access Programme (EAP) in England and Wales. Kyowa Kirin estimates, based on NHS clinical practice, the patient population suitable for burosumab will be at the lower end of the estimated prevalence range of 291 to 578 in adults (please see details on this epidemiological estimate presented under Section ““**Questions for consultation**	Thank you for your comment. Following the scoping workshop, the population listed in the background has been updated.

[1] Adults presenting with progressive musculoskeletal disease, debilitating symptoms, including but not limited to pain, stiffness and fatigue with a substantial impact on their quality of life, those who have non-healing or slow healing fractures or pseudofractures, those who have undergone or require surgeries (such as orthopaedic, dental or spinal surgery) for 3 months pre-surgery or post-surgery until 6 months after surgical wound healing and, finally, those who have persistent symptoms associated with XLH despite prior treatment with conventional therapy.

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		No other subgroups of patients have been identified that should be considered separately during this appraisal.	
	Brittle Bone Society	2500 seems excessive and not in line with current publications where the prevalence is estimated to be much lower based on NHS figures.	Thank you for your comment. Following the scoping workshop, the population listed in the background has been updated.
	Metabolic Support UK	The population defined is accurate. The scoping should consider if the children who are currently receiving Burosamab and would be transitioning into adulthood in the next few years constitute a sub group. They, along with any adult patients who have had Burosamab, may have fewer or improved symptoms than adults who were on the traditional conservative therapy and may continue to benefit from ongoing Burosamab therapy. .	Comment noted.
	XLH UK	The whole adult XLH population is defined correctly. It is worth noting that there may be some adults among the XLH population who are presented with fewer symptoms however they are and will forever be hypophosphataemic therefore we believe that burosumab would still be highly beneficial at normalising serum phosphate for that population to prevent any inevitable skeletal crisis later in life.	Comment noted.
	NHS England	Our numbers (collated via a survey) indicate a smaller population (c.280) than that given in the scope (2,400) but it may be that are severely affected individuals.	Thank you for your comment. Following the scoping workshop, the population listed in the

Section	Consultee/ Commentator	Comments [sic]	Action
			background has been updated.
	Metabolic Bone Centre, Sheffield Teaching Hospitals NHS FT	Yes	Comment noted.
	Royal National Orthopaedic Hospital NHS Trust	The population is clearly defined. Subgroups that could be analysed separately include patients undergoing orthopaedic surgery, or those with fractures/pseudofractures.	Thank you for your comment. No action required.
	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	Yes The appraisal should apply to the entire population without subdivision	Thank you for your comment. No action required.
	University Hospitals Bristol and Weston NHS Foundation Trust	I am concerned the estimate of 2,500 adults in the UK with XLH seems quite high and may not reflect the numbers we are seeing in clinical practice. We have 17 adult XLH patients under our care, 10 of whom have started burosumab. We currently accept referrals across the whole South-West and	Thank you for your comment. Following the scoping workshop, the population listed in the

Section	Consultee/ Commentator	Comments [sic]	Action
		have received referrals from Bath and Oxford. This treatment may therefore sit better as a highly specialised technology?	background has been updated.
Comparators	Kyowa Kirin (company)	The response below covers the following question in the draft scope: • Which treatments are considered to be established clinical practice in the NHS for XLH? Kyowa Kirin agrees that the appropriate comparator for burosumab's appraisal is established clinical management without burosumab. Currently available treatments for XLH in adulthood are limited and suboptimal. The only available pharmaceutical option is oral phosphate (administered several times daily) and active vitamin D. However, oral phosphate is unable to address the pathophysiology of XLH (FGF23-induced hypophosphataemia); has a weak and poorly understood benefit/risk profile without compelling evidence; is poorly tolerated; has associated adverse health consequences and requires close monitoring. Given the adverse consequences of exposure to this treatment, clinicians have only prescribed it to some symptomatic adults with XLH, and on an intermittent basis (European Best Practice Guidance, 2019) (6). The prescribing of this therapy appears to be non-standardised across healthcare providers.	Thank you for your comment. Following the scoping workshop, the background has been updated.
	Brittle Bone Society	YES	Comment noted.
	Metabolic Support UK	Surgeries should be considered in more detail alongside the conventional therapy of (vitamin D and phosphate). We are aware of concerns around adherence to conventional standards of care. Conventional therapy is often considered supportive by our patients rather than curative. Patients have to undergo a multitude of surgeries in their lifetime as a result of osteomalacia.	Thank you for your comment. No action required.

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	XLH UK	There is no standard level of care for adults with XLH as the conventional supplements are believed to have little benefit on fracture healing and or bone pain. Although they are normally given pre- postoperative care, there are dangers of having conventional supplements. As a result they require frequent monitoring from specialised clinicians. Comparatively, surgery is common among adults with XLH as an option to improve mobility and quality of life.	Thank you for your comment. No action required.
	NHS England	Yes. The comparators are accurate and can be described as best alternative care.	Comment noted.
	Metabolic Bone Centre, Sheffield Teaching Hospitals NHS FT	Conventional treatment is described but the difficulties and complications are not really mentioned. Phosphate supplements cause GI symptoms leading to poor adherence and can cause secondary hyperparathyroidism. Treatment with vitamin D analogues can cause hypercalciuria, nephrocalcinosis and renal impairment. The dose is sometimes difficult to adjust Treatment is given usually to patients with pseudofractures and/or abnormal biochemistry with high alkaline phosphatase. Patients may also be treated because of less specific symptoms such as bone pain, stiffness and fatigue Not all adult patients require treatment	Thank you for your comment. Following the scoping workshop, the background has been updated.
	Royal National Orthopaedic Hospital NHS Trust	Not all adults are currently treated. At present, treatments are targeted to adults with symptoms or those with complications. Some patients may be seen in a specialist centre, but some may also be under local care. Treatments include oral phosphate supplements and activated vitamin D analogues (calcitriol, alfa calcidol).	Thank you for your comment. Following the scoping workshop, the background has been updated.

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	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	There is a wider clinical consensus regarding the principles of treatment than implied in the current text. These would be the use of active vitamin D analogues with or without phosphate supplementation. The issue over whether to use phosphate or not is primarily driven by the views of a single, albeit influential, individual and it would be generally considered usual practice for this to be given. It must also be remembered that at the completion of linear skeletal growth many young adults with XLH will spend a period of time when they do not require medical treatment but symptomatic disease almost always necessitates the reintroduction of therapy. I am not sure if this is directly a comparator but some consideration needs to be built into the cost effectiveness model of the not inconsiderable costs of treating complications such as surgery for fractures, deformity, nerve compression and hyperparathyroidism.	Thank you for your comment. No action required.
Outcomes	Kyowa Kirin (company)	The response below covers the following question in the draft scope: • Are the outcomes listed appropriate? Kyowa Kirin believes the outcomes listed in the draft scope are incomplete. The following clinically important and patient-relevant outcomes should be included in the final scope in addition to what has been listed already: 1) increase in serum phosphate concentrations (above the LLN [2.5 mg/dL]) 2) pseudofracture healing 3) measure of physical function Kyowa Kirin considers that the following outcomes listed in the draft scope should not be included for adults: tooth loss, dental pain, intracranial pressure and craniosynostosis. Whilst dental health issues represent a significant burden for adults with XLH, many of the complications present in adults are as a consequence of the chronic low levels of phosphate in utero and	Thank you for your comment. Following the scoping workshop, the outcomes have been updated.

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		childhood and this it is unlikely to be reversible in adulthood. Intracranial pressure and craniosynostosis are common manifestations of XLH in children but are not relevant for burosumab's appraisal in adults	
	Brittle Bone Society	In our opinion - sleep, fatigue, mobility and surgical interventions and severe shortage of access to dentistry, should have been listed, but that possibly comes under QOL.?	Thank you for your comment. No action required.
	Metabolic Support UK	These outcome measures are appropriate, however, the mental health aspects within the health-related quality of life (for patients and carers) should be explicitly reviewed. Consideration should also be given to the disruptions and burden caused by current treatment options: such as regular intake of Vitamin D (4-6 times a day) causing disruption to sleep, daily activities and thus the quality of life of patients and surgeries (including pre and post-surgical care).	Thank you for your comment. No action required.
	XLH UK	We believe that comorbidities and depression associated to living with and or inheriting and or passing on XLH should be considered as an outcome as the progressive life-long burden can amounts to a reduced quality of life.	Thank you for your comment. No action required.
	NHS England	Yes. He outcome measures listed capture the most important health-related benefits.	Comment noted.
	Metabolic Bone Centre, Sheffield Teaching Hospitals NHS FT	Key outcomes should include pseudofractures or Looser's zones on imaging, and/or fractures Phosphate levels should also be included	Thank you for your comment. No action required.

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	Royal National Orthopaedic Hospital NHS Trust	Craniosynostosis and raised intracranial pressure are more appropriate outcomes for paediatric patients rather than adults.	Thank you for your comment. Following the scoping workshop, the outcomes have been updated.
	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	A lot of the outcomes listed are relevant to paediatric practice but not XLH in adults. These include: • Motor skills • Raised ICP • Craniosynostosis The primary dental problem seen in adults would be more precisely defines as dental abscess rather than tooth loss or pain which can ensue. Important outcome measures for adults should also include (in addition to the others already identified): • Restriction of joint movement • Other nerve compression, not just spinal cord • Development of hyperparathyroidism	Thank you for your comment. Following the scoping workshop, the outcomes have been updated.
Economic analysis	Kyowa Kirin (company)	The use of cost comparison methodology for this topic is not appropriate as treatment with burosumab has been shown to be more effective than 'established clinical management'.	Thank you for your comment. No action required.
	Brittle Bone Society	Not entirely clear what you are expecting us to comment on.	Comment noted.

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		You state the time horizon should be sufficiently long to reflect any differences in costs or outcomes between technologies being compared – but unclear what it is being compared against?	
	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	The time horizon should be whole lifetime	Thank you for your comment. No action required.
Equality and Diversity	Kyowa Kirin (company)	The rarity, complexity and burden of the disease in adults is at least the equal of that in children. It is important therefore that burosumab is appraised through the NICE HST programme to ensure that adult patients with XLH are not disadvantaged due to the rarity of their condition, given the STA programme's unsuitability for assessing treatments for very rare diseases. Otherwise, Kyowa Kirin does not think that the remit and the scope need to change to meet other equality issues.	Thank you for your comment. NICE's Topic Selection Oversight Panel has considered this topic and the final decision was made to route this topic. No action required.
	Brittle Bone Society	In response to this we would ask some questions: How many people from the XLH community (as in people who are diagnosed and live with the condition) do you plan to invite and engage with around the table? I assume the ratio during consultation in attendance will be approx. 5 clinician's reps represented to 1 patient rep.	Comment noted. Please see the NICE guide to the technology appraisal process for more information about patient expert representation.

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	NHS England	The scope does not need changing.	Comment noted.
	Metabolic Bone Centre, Sheffield Teaching Hospitals NHS FT	No concerns	Comment noted.
	Royal National Orthopaedic Hospital NHS Trust	No changes needed.	Comment noted.
	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	No specific equality issues other than those related to the disability caused by XLH itself	Comment noted.
Other considerations	Kyowa Kirin (company)	The higher risk of mental illness among adult patients with XLH, carer and family burden, and capacity for wider societal participation (for example in the workplace) should also be considered within burosumab's appraisal.	
Innovation	Kyowa Kirin (company)	Burosumab is a first in class disease-modifying treatment, in the form of a fully human monoclonal IgG1 antibody, used as monotherapy. It is indicated	Comments noted. The company will have the opportunity to expand

Section	Consultee/ Commentator	Comments [sic]	Action
		for treatment of XLH in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults. On 31st January 2017, burosumab received a 'Promising Innovative Medicine' (PIM) designation from the Medicines and Healthcare products Regulatory Agency (MHRA), confirming its potential to address a high unmet need in children with a seriously debilitating condition [reference EAMS 16508/0001]. Burosumab has already been shown to be a life-changing treatment for children (over 1 year of age) and young people with growing skeletons, and for that reason, NICE has previously recommended burosumab for the treatment of XLH for this group of patients [HST8]. Treatment with burosumab for this group has been limited to a small number of highly specialised paediatric centres that were previously part of the European Reference Network for rare bone diseases. In addition, burosumab is an important new treatment ("a step-change") for XLH in adults due to its novel mechanism addressing the pathophysiology of the disease, its clinical efficacy, and its safety profile. It is expected that burosumab will be used on a lifelong basis, to maintain the restored phosphate homeostasis. Evidence from a large, global clinical trial of adults with XLH who were symptomatic, despite years of previous exposure to conventional therapy, showed that treatment with burosumab improved serum phosphate levels, providing a rapid and sustained improvement in bone quality and in symptoms, driving disease modifying effects, with improved healing of fractures and pseudofractures, accompanied by a well-tolerated profile (7). The use of burosumab in adults is expected to bring significant gains in other areas such as work productivity and improvements in mental health and social functioning.	on the innovative potential of this technology in its submission and this will be considered by the appraisal committee.

Section	Consultee/ Commentator	Comments [sic]	Action
	Brittle Bone Society	Yes as there are no treatment alternatives that we are aware of.	Thank you for your comment. No action required.
	Metabolic Support UK	An MSUK consultation with members representing those living with XLH disease found patients consider Burosumab to be a 'step-change' in treatment options. The patients who have been on the early access program have said that it provides significant and substantial potential for improvement in disease management.	Thank you for your comment. No action required.
	XLH UK	XLH UK has found that among it's 160+ members across England, they have considered burosumab to be a 'step-change' in treating their XLH. Burosumab is a first in targeting the underlying cause of phosphate wasting and has shown to not only improve fracture healing and bone pain (clearing fatigue) but also slow if not prevent enthesopathy in adult life. This treatment has the potential to mitigate the some of the most cruel symptoms adults are faced with throughout their lives.	Thank you for your comment. No action required.
	Metabolic Bone Centre, Sheffield Teaching Hospitals NHS FT	Yes, definitely a step change – this is the first treatment that treats the causative abnormality in this disease. It is proven to be effective in these patients and it is easier to administer. As mentioned before, patients do not always adhere to current treatments due to side effects and monitoring is difficult. Patients are at risk of hypercalciuria with the current treatments Yes, the healing of a pseudofracture usually benefits symptoms and should be captured Will health care use be included in the economic analysis? Should be accessible from UK Clinical Research Database and published data on pseudofractures	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal National Orthopaedic Hospital NHS Trust	Burosumab is an innovative and novel treatment for management of XLH	Thank you for your comment. No action required.
	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	This is the first intervention which provides a specific targeted treatment for XLH. Experience in children have shown it to be a complete “game changer” and it can be anticipated to have a similar step change in the management of adults with XLH, especially those with clinical complications.	Thank you for your comment. No action required.
Questions for consultation	Kyowa Kirin (company)	The response below covers the following questions in the draft scope: • Is the adult population of adults with XLH in England accurate?: “No” • Are adults with XLH treated in a small number of specialist centres?: “Yes, please see detailed response below”. • What proportion of adults with XLH were diagnosed in adulthood?: “A small minority as it is picked up mainly in childhood”. As noted above, burosumab for the treatment of XLH in adults should be assessed under the NICE HST programme rather than the STA process. This topic meets all the HST criteria (according to HST methods process and guide). Specifically: **1) The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS;**	Comments noted. After considering information received from consultation and comments from the scoping workshop it was agreed that the appropriate route for burosumab was as a single technology appraisal. Please see the HST checklist for further details.

Section	Consultee/ Commentator	Comments [sic]	Action
		The estimate of prevalence of the XLH adult population in England stated in the draft NICE scope (2,500) is inappropriate, out of date and misleading. Furthermore, this estimate is not referenced. Based on the latest evidence, Hawley et al (2020) (4), the adult XLH population in England would range from 291 to 578 adults in total, as outlined hereafter. This range of adult population with XLH correlates with the Hawley et al (2020) (4) estimate of children cases (range between 172 to 200) and Kyowa Kirin data shows [redacted] children being treated on burosumab with the access of HST8. Kyowa Kirin believes that Hawley et al. (2020) results represent the most appropriate and robust estimates of XLH prevalence for this appraisal as it is both UK-based and focuses on prevalence of adults in contact with the healthcare system. Kyowa Kirin data: • the number of adult XLH patients in the early access programme [redacted] • adults with XLH in the XLH registry (NCT03193476) [redacted] **<u>Further detail on prevalence estimates:</u>** The prevalence estimate for NICE's draft scope of 2,500 adults is unreferenced. It is presumed that it is estimated from data collected in 2002 from children (<15 years) in Southern Denmark and extrapolated to adults. The estimated prevalence of XLH in children was 4.8 per 100,000, based on 12 identified cases (8). As mentioned above, more accurate data, specifically in adults, is now available from a published UK-based study (Hawley et al, 2020). This study is based on data collection through the Clinical Practice Research Datalink	

Section	Consultee/ Commentator	Comments [sic]	Action
		(CPRD), a large UK primary care database and was published in 2020. This provides a significantly more detailed, up to date and methodologically robust estimate of XLH cases in a UK setting. For the most recent data collected in this study (2012-2016), the less conservative analysis of XLH prevalence (13.3 per million) suggests a population size of 578 adults with XLH in England[2] which is an overestimation of the true prevalence figure (cases in this study were not confirmed by TmP/GFR and/or genetic testing). It is also important to highlight that, based on this UK epidemiological study (Hawley et al, 2020) and for the latest data collected (2012-2016), prevalence of children deemed as likely or very likely to have XLH was reported as up to 14.6 [95% CI, 8.1–26.6] per million, which would predict 172 children with XLH in England could be suitable for treatment with burosumab. Using the same case definition for adults (likely or very likely to have XLH), it is anticipated that up to 291 adults may require treatment with burosumab (prevalence estimates in the paper was reported as 6.7 [95% CI, 4.5–10.2] per million). Based on NHS clinical practice (ongoing early access programme) this estimate may be even lower for suitability to treat with burosumab. Furthermore, if the prevalence of XLH is likely to be similar between children and adults due to the genetic and lifelong nature of this condition with even a lower proportion of adults likely to be treated with burosumab compared to children; if similar to children, XLH in adults is a distinct genetic condition associated with profound morbidity and, burosumab is the only treatment targeting the pathophysiology of XLH, then it would be expected that the NICE HST criteria are equally applied to the appraisal of burosumab for both	

[2] Using ONS Data for adults in mid-2016 (England)

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		children and adults with XLH. Therefore, burosumab for the treatment of XLH in adults should not be assessed through the STA programme. **<u>Treatment with burosumab in highly specialised centres:</u>** Similar to the situation in children, it is expected that burosumab will only be administered in highly specialised centres. There is a limited number of expert clinicians with the necessary training and experience in rare metabolic bone diseases to appropriately identify and manage patients with X-linked hypophosphataemia. Adults with XLH require to be diagnosed and managed by a multidisciplinary team (MDT) capable of addressing the complex nature of the condition. There are ongoing initiatives with NHS England & Improvement (NHSE&I) to review specialised centres for rare bone disorders, based on previous European Reference Networks for Rare Endocrine Disorders (ERN-ENDO) or Rare Bone Disorders (ERN-BOND) within the NHS. These are currently being discussed with Endocrinology and Rheumatology Clinical Reference Groups (9,10). Currently, 5 specialised centres are enrolled in burosumab's Early Access Programme. Kyowa Kirin is also engaging with NHS England's Highly Specialised Services team to ensure appropriate and consistent access to healthcare for adults with XLH as the network of specialised centres develops. **2) The target patient group is distinct for clinical reasons;** The target group of adults with XLH who will be eligible to receive burosumab is a clinically distinct group with a complex array of morbidities. These adults will have a confirmed diagnosis of XLH who have evidence of progressive disease due to a lifetime of chronic hypophosphataemia and are experiencing debilitating, persistent symptoms despite prior treatment with conventional therapy.	

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		As noted, XLH is a lifelong phosphate wasting disease. In adults, chronic low serum phosphate levels has caused multiple musculoskeletal morbidities including fractures, pseudofractures, osteoarthritis, enthesopathy and spinal stenosis, leading to gait abnormalities as well as hearing deficits and dental abscecces. Many adults have also developed nephrocalcinosis and hyperparathyroidism secondary to lifetime exposure to oral phosphate and active Vitamin D. **3) The condition is chronic and severely disabling;** As previously described, adults with XLH experience a progressive accumulation of morbidities such as fractures, pseudofractures, osteoarthritis, enthesopathy and spinal stenosis, gait abnormalities as well as hearing deficits and dental abscesses. Chronic symptoms include bone and joint pain, stiffness, fatigue leading to impaired physical function and decreased mobility. A UK multi-center prospective study (the Rare and Undiagnosed Diseases Study [RUDY]) (Forestier-Zhang et al, 2016) (11) assessed health related quality of life outcomes in adult XLH patients. A total of 109 study participants fully completed the EQ-5D-5L questionnaire (response rate 63%). Pain/discomfort was the most problematic domain for participants with XLH, with 67% reporting moderate or severe problems. Based on the EQ-5D-5L data, this study reported a utility score of 0.648 (SD 0.29) for adult XLH patients. This utility score indicates the significant impairment and burden adults with XLH have. The burden of XLH is highly physical, driving substantial emotional and social, burden. Furthermore, this negative impact is not only experienced by those affected by the disease, but also by their families given the X-linked (genetic) nature of the disease, which means multiple family members can be affected across several generations.	

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		4) The technology is expected to be used exclusively in the context of a highly specialised service; Due to rarity of disease and its complexity of manifestations in adults, good quality care is best provided by experienced expert clinicians. In addition, as a rare X-Linked genetic condition, XLH presents a commissioning challenge in that provision of care is likely to be centred around family-based clusters. The current adult early access programme is based on provision of burosumab in five expert centres. Involvement of other medical specialities is dependent on service setup and multidisciplinary team (MDT) working within the National Health Service (NHS) England-recognised specialist centres for rare bone disorders. Therefore, it is expected that burosumab as an innovative treatment for a rare disease will be offered in the context of a highly specialised NHS service, following key priorities recently set by the UK Rare Disease Framework (January 2021) (12). **5) The technology is likely to have a very high acquisition cost;** This criterion is also met as burosumab is currently available for the treatment of children, it is already considered a high cost technology and is only accessible in England via Blueteq. **6) The technology has the potential for life long use;** Burosumab is an important new offering in the treatment of XLH in adults due to its novel mechanism, its clinical effectiveness and its tolerability profile. It is expected that burosumab use in adults will be ongoing to restore and maintain phosphate homeostasis. **7) The need for national commissioning of the technology is significant;**	

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		Due to rarity of disease and its complexity of manifestations in adults, good quality care is best provided by experienced expert clinicians. In addition, as a rare genetic condition, XLH presents a commissioning challenge in that provision of care is likely to be centred around family-based clusters. This would place a significant burden on local resources if no national approach was available. In recognition of these challenges, services for adults with XLH are already commissioned nationally and active discussions are ongoing regarding the formal establishment of a highly specialised service to support improve coordination of care and consistency in prescribing decisions. **Summary** There are no available treatments to restore the driver of the XLH disease (phosphate homeostasis) and there is a high disease severity, which drives a high 'individual unmet need'. By targeting the pathophysiology of FGF23-induced hypophosphataemia, burosumab offers a unique opportunity for a new treatment paradigm for adults with XLH by providing immediate and sustained improvement in debilitating symptoms, by healing fractures and pseudofractures, and possibly reducing incidence of new fractures/ pseudofractures. We are currently working with patient groups, expert clinicians and NHS England and Improvement to consider how these centres could be determined, as part of a wider initiative to define a suitable highly specialised service framework for adults with rare bone disorders, including XLH. This work is aligned to the priorities recently set out in the UK Rare Disease Framework (January 2021) (12), which included a focus on improving the coordination of care for rare conditions and improving access to specialist care, treatments and drugs.	

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		Kyowa Kirin strongly believes that burosumab satisfies all the HST criteria and that it should be appraised under the HST programme which would be both procedurally appropriate and fair for the adult XLH community.	
	Brittle Bone Society	Switching between this document and looking again at the Appendix Scoping document it is not easy to determine which of the questions for consultation overall, are not listed above. *(doing this at home, working on a small laptop in less than usual and non office conditions with easier access to better computer equipment).* As with many other rare bone conditions in the rare category – XLH has unfortunately got NO related guidelines; NO public health guidance/guidelines; NO related quality Standards and NO related NICE pathways. E.g. No clear overall qualified consensus on best treatments/pathways. *NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).* **We understood the STA process to be for more common conditions of higher population numbers and as XLH sits in the rare disease area, that it may have gone through the Highly Specialised Route.**	Thank you for your comment. No action required.

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	Metabolic Support UK	This technology was evaluated through the HST programme in 2018. When it was being appraised for children. MSUK understand that this is an indication for the same condition in the adult population and it is unclear why this should be routed through the STA programme. We have concerns about the consideration of patients who have been receiving Bursomab treatment since the NICE recommendation in 2018.	Thank you for your comment. No action required.
	XLH UK	Our last comment is with regards to the STA pathway that burosumab appears to be heading towards. We recognise that the adult XLH population in England is small at 1 in every 90,000 individuals. XLH is a progressive disease that currently requires multidisciplinary care and has significant impact on the patient, carer and family. The associated costs that an XLH patient has on the NHS and productivity in society through the need of repeated surgeries, complex after care, home adaptations and life-long oversight from specialist rheumatologists, endocrinologists and orthopaedic surgeons we assume would be high and demanding on the health service. We would argue that burosumab could eventually be prescribed and monitored by a local clinician without a dependency on specialist services while mitigating the need for surgery. Therefore we believe the positive impact burosumab has is substantial for the NHS and life-changing for the patient and community.	Thank you for your comment. No action required.
	Metabolic Bone Centre, Sheffield Teaching Hospitals NHS FT	Site of treatment – mainly specialist centres, often using hub & spoke approach with local centre Subgroups who may benefit most – those with clinical and/or radiological evidence pseudofractures; patients undergoing orthopaedic or dental/max-fax surgical procedures	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Nuffield Orthopaedic Centre	Is the adult population of adults with XLH in England accurate? *It is incorrect to say XLH is equally common in both sexes. It is commoner in women due to the X-linked dominant nature of inheritance* *The quoted 2,500 adults is based on rates per 10,000 birth data and likely too high. Hawley et al. has shown reduced survival in adults with XLH. In our clinical experience XLH is much less common. Public Health England performed a survey of all major Rare bone disease centres for children and adult separately that included all cases and complex cases with hereditary hypophosphataemia. That should give a sense check for the clinically diagnosed population of adults with XLH.* Are adults with XLH treated in a small number of specialist centres? *This is inconsistent. While specialist centres will see large cohorts of patients, it is likely that individual cases will be seen only in district general hospital non-specialist endocrine and rheumatology clinics or as needed by orthopaedic units.* What proportion of adults with XLH were diagnosed in adulthood? *Few adults are diagnosed in adulthood, usually because they have been misdiagnosed with ankylosing spondylitis. Most are lost to followup after they leave paediatric services.* Which treatments are considered to be established clinical practice in the NHS for XLH?	Thank you for your comment. Following the scoping workshop, the background has been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		Oral phosphate and activated vitamin D (either alfacalcidol and calcitriol) are established treatment given either routinely to adults with XLH, when they moderate symptoms or only in specific circumstances such as pseudofracture or around the time of orthopaedic surgery. A watch and wait policy is common. Are the outcomes listed appropriate? *Fractures should include complete fractures and pseudofractures* *Pain should be rephrased as musculoskeletal pain* *motor skills is unclear, do you mean mobility* *tooth loss and infection* *Hearing should be separated from neurological complictions* *Renal function-is chronic kidney disease better term or nephrolithiasis* *Parathyroid levels – hyperparathyroidism requiring surgery.* Are there any subgroups of people in whom burosumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? *There are two main subgroups. Adults with clinically apparent complications of XLH leading to moderate symptoms where the aim is reduce the progress and impact of morbidity. Adults with minimal complications of XLH where the aim is to prevent morbidity. Other specific subgroups include those with pseudofractures.*	

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		NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which burosumab will be licensed; *Not to my knowledge* • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; *There would need to be geographical coverage of England by the Rare bone network so distance for travelling is not a deterrent to access as Hawley et al have shown adults with XLH are more likely to be socially deprived.* • could have any adverse impact on people with a particular disability or disabilities. *Not to my knowledge.* Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. *The committee could ensure the recipients of burosumab are representative of all levels of social deprivation.*	

Section	Consultee/ Commentator	Comments [sic]	Action
		Do you consider burosumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? *Burosumab is an innovation game changer for the management of XLH. Due the nature of the trial only a short period of controlled observation was permitted but even this demonstrated significant improvements in many dimensions. If proven safe in long term use, Burosumab could be the curative treatment for XLH if given across the lifetime.* Do you consider that the use of burosumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? *As individuals with XLH are live in pain and discomfort from birth, it is likely they have overestimated their perceived quality of life prior to initiation of burosumab, making any change in QoL difficult to interpret. Many patients have increased their level of activity substantially until they are pain. Benefits in vitality are not well captured nor fatigue and opioid use.* Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. *Personal statements from patients, data from clinical trials, observational cohorts and big data.*	

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		To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. *One barrier may be the need for a genetic diagnosis of XLH. Given the likely costs of treatment, it would seem prudent to include XLH testing in the NHS Genetic testing directory.* NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made. *If the target population is to be those adults with moderate symptoms an HST approach may be more appropriate given the rarity of the disease* • • Would it be appropriate to use the cost comparison methodology for this topic? *Given there is no NHS care pathway, there is no standard alternative care pathway or therapy for comparison* • • Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? *No*	

Section	Consultee/ Commentator	Comments [sic]	Action
		• • Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? *No, the primary outcome for the trial was a biochemical repletion in phosphate not a clinical outcome.* • • Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? *Ongoing observational studies on the burden of XLH are due in the next year.*	
	Royal National Orthopaedic Hospital NHS Trust	The paediatric use of the drug is covered by a Higher Specialised Technology Guidance, yet the adult used is being evaluated as Single Technology Appraisal. Can the rationale for this be explained?	Thank you for your comment. No action required.
	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	Is the adult population of adults with XLH in England accurate? This is broadly correct but may be slightly low Are adults with XLH treated in a small number of specialist centres? Definitely not. As with many metabolic bone diseases there is no single speciality which "owns" the management of patients with XLH and they may be seen by endocrinologists, rheumatologists or nephrologists depending on local custom and practice. For many patients without major complications, they will be manged all their life. If they develop complications, they are likely to be referred into a more specialist regional centre. These are usually run by endocrinologists or	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		rheumatologists although some have a significant input from chemical pathologists. There are between 15 – 20 such centres around England. What proportion of adults with XLH were diagnosed in adulthood? See above: no more than 20%. These are usually patients with mild metabolic disease who develop problems in later life. Which treatments are considered to be established clinical practice in the NHS for XLH? See above Are the outcomes listed appropriate? See above Are there any subgroups of people in whom burosumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? It is unlikely that an expensive treatment such as burosumab would prove cost effective in adults with XLH which is well controlled on conventional treatment and so its use should be examined in those with complicated disease where the additional benefits may be worth paying a premium price. Such patients might be broadly defined by the access criteria currently applied to the early access scheme such as: - intractable pain - neurological complications - fracture	

Section	Consultee/ Commentator	Comments [sic]	Action
		- need for orthopaedic surgery	
Additional comments on the draft scope	Kyowa Kirin (company)	No	Noted.
	Society for Endocrinology and Central Manchester University Hospitals NHS Foundation Trust	Whilst burosumab has been made available to clinicians in England treating adults with XLH as part of an early access scheme by the manufacturer the different regional offices of NHSE appear to have taken a different attitude to this scheme. As a result, there is at present uneven access across the country and definitive guidance from NICE would be welcome to eliminate any such inequity.	Thank you for your comment. No action required.