NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Burosumab for treating X-linked hypophosphataemia [ID1151]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Consultee and commentator comments on the Evaluation Consultation Document** from:
   - **Kyowa Kirin**
     - **Appendix A** – trial data
     - **Appendix B** – PAS analysis
   - **Birmingham Children's Hospital NHS Foundation Trust and British Paediatric & Adolescent Bone Group joint response**
   - **Metabolic Support UK**
   - **XLH UK**

   Please note 'No comments' responses were received from the Department of Health and Social Care and NHS England

3. **Comments on the Evaluation Consultation Document from experts:**
   - **Prof Zulf Mughal**, Consultant in Paediatric Bone Disorders – clinical expert, nominated by Royal Manchester Children's Hospital

4. **Comments on the Evaluation Consultation Document received through the NICE website**

5. **Evidence Review Group critique** of the company ECD response prepared by Kleijnen Systematic Reviews

6. Evidence Review Group critique - **Addendum**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Burosumab for treating X-linked hypophosphataemia in children and young people

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
Kyowa Kirin	Kyowa Kirin are grateful for the opportunity to provide additional evidence to address the uncertainties the committee noted in the ECD. In the ECD, having considered the view of patients and clinical experts, the committee concluded that burosumab has the potential to significantly improve patients' quality of life in the long term by modifying the disease during childhood. In this response, we provide: • The results of the recently reported Phase 3 study comparing burosumab with conventional therapy (CL301) (Appendix A) • Evidence supporting the likely long-term disease progression during adulthood • An updated economic analysis including a patient access scheme that improves the cost-effectiveness of burosumab (Appendix B). **Phase 3 study results** The Phase 3 study addresses concerns around the clinical evidence presented in the original submission, which consisted only of single arm studies (CL201 and CL205) and historical controls (for CL201 only). CL301 was a Phase 3 randomised, controlled study in patients aged 1 to 12 years, comparing burosumab to conventional therapy, which is the UK current standard of care. This evidence significantly reduces the uncertainty around the clinical effectiveness of burosumab in children aged 1 to 12 years, and demonstrated that burosumab is significantly more efficacious than conventional therapy. Clinical experts were clear during the committee meeting that they believed burosumab would be at least as efficacious, if not more so, in patients aged 13-17, because this is the age of the greatest skeletal growth. Whilst we acknowledge that RCT evidence is not available within this age range, we	Comments noted. The committee considered the results from the CL301 study in its evaluation of burosumab. See section 4.8 of the final evaluation document (FED). The committee recognised that people may benefit more from burosumab treatment between 11 and 16 years, but emphasised that there was no evidence in young people aged 13 to 17 years. See section 4.9 of the FED. The FED has been amended to describe the baseline Rickets Severity Score (RSS) in the CL210, CL205 and CL301 studies.

Consultee	Comment	Response
	believe the ECD fails to acknowledge both the unmet need and the clinical experts' expectations for this age group. The ECD incorrectly states that only children with a Rickets Severity Score (RSS) of 1.5 or above were included in the CL201 and CL205 studies. We would like to clarify that the Phase 2 studies for burosumab included paediatric patients across a wide spectrum of disease severity including those with less severe rickets (RSS total score ranged from 0.0 to 4.5 in CL201 and from 1.0 to 6.5 in CL205). The CL301 study enrolled subjects with an RSS of 2.0 or greater, to best demonstrate a treatment effect and maximise the ability to detect change, as recognised within the ECD. This has implications for the economic analysis since incorporating evidence for only those with an RSS>2.0 would not enable a full simulation of the long-term impact. Consequently, the results of the CL301 study have been included within the economic analysis by combining all the Phase 2 and 3 study data for burosumab, as well as utilising the UK chart-review data and the Phase 3 control arm for the conventional therapy arm. Incorporating this additional data significantly reduces the uncertainty around the cost-effectiveness.	
Kyowa Kirin	**Expected long-term outcomes during adulthood** During the committee meeting, clinical experts explained that even if bone defects are corrected in childhood, people will continue to have symptoms and be at risk of new bone defects into adulthood. The ECD states that the committee understood this to mean that burosumab would not affect the progression of bone manifestations of XLH during adulthood (for example, increased risk of osteomalacia and accompanying stress fractures and pain) or other ongoing aspects of the condition such as metabolic effects of low phosphate (for example, muscle weakness and fatigue). As a consequence, the committee concluded there would be long term benefits from fixing or preventing childhood skeletal deformities, but that burosumab would not affect other aspects of XLH in the long term. We would accept that, following discontinuation of burosumab, adults would over time experience ongoing aspects of XLH such as metabolic effects of low phosphate. However, we would like to further illustrate the broader impact of fixing or preventing childhood skeletal deformities on life-long quality of life, compared to ongoing aspects of disease in adulthood, such as osteomalacia. As noted by one of the patient representatives at the first committee meeting, the detriments in adult quality of life are very much associated with	Comment noted. The committee considered the long-term benefit of childhood treatment with burosumab. The impact of XLH during adulthood was discussed with the clinical and patient experts during the committee meeting; the committee understood that painful symptoms of XLH result from established bone deformities. The committee concluded that there would be long-term benefits from preventing or correcting skeletal deformities, but agreed that burosumab could not affect other aspects of XLH long-term after treatment is stopped. For more information see sections 4.1 and 4.15 of the FED.

Consultee	Comment	Response
	deformities. The uncertainty highlighted by the committee is the effect of osteomalacia on quality of life in the absence of such previous deformities. Painful symptoms occurring in adults with XLH are caused by bone deformities and associated joint inflammation and not osteomalacia per se (Marie and Glorieux, 1982). A study – co-authored by Glorieux, one of the leading authorities on metabolic bone disorders – showed that, despite the absence of symptoms in some adult XLH patients, they still have active bone disease characterised by moderate to severe osteomalacia. In addition, bone pain and associated symptoms in osteomalacia usually result from decreased calcified bone volume. In patients with XLH, decreased calcified bone volume is not detected despite the presence of moderate to severe osteomalacia (Marie and Glorieux, 1982). Avoiding or correcting skeletal deformities is expected to result in reduced osteoarthritis, stiffness and enthesopathy, and consequently reduced pain and improved mobility throughout their lifetime. Nearly half of adults have undergone some form of corrective surgery of skeletal abnormalities that originated during skeletal growth (Chesher et al., 2018). It is therefore expected that the need for corrective surgery will be much reduced or avoided, and that operations that may be required later in life (e.g. arthroplasties) would also be delayed or avoided. It is expected that this type of surgery will be greatly reduced or will no longer be required if the patient received burosumab in childhood. Bone remodelling continues throughout life. In patients with XLH this means that new bone being laid down may not be fully mineralised, leading to a reduction in bone quality. The clinical effects of this gradual reduction of bone quality in adult life will not become apparent until it reaches a clinically meaningful threshold. Patients with XLH who have had no previous disease-modifying treatment can be expected to reach adulthood with significantly reduced bone quality as a result of suboptimal phosphate control and will therefore reach any such threshold earlier than patients who have had such treatment. Therefore, in a cohort of adults managed with standard of care it would be expected that, relative to those treated with burosumab, they would start adulthood with much lower bone quality, in addition to any skeletal deformities present from childhood. These expectations were agreed in consultation with Prof Colin Farquharson, an expert in skeletal biology (Box 1). Taken together, progression of symptoms and associated decline quality of life following discontinuation of burosumab is expected to be more delayed than current treatment.	

Consultee	Comment	Response
	Box 1. Scientific statement from Prof Colin Farquharson, Professor of Skeletal Biology	
	The progression of X-linked hypophosphatemic rickets (XLH) in children leads to muscle weakness, short stature, lower limb deformities and poorly mineralised bone. The primary cause of the skeletal defects is defective mineralisation of newly formed bone matrix (osteoidosis). Poor mineralisation is caused by elevated circulating levels of FGF23 which drives excessive phosphate excretion resulting in low phosphate levels. In the growing child impaired mineralisation occurs at all bone forming surfaces (osteomalacia) including the chondro-osseous junction at growth plate which results in stunted and abnormal growth of the long bones (endochondral ossification). This in turn leads to lower-extremity bowing, altered gait and abnormal biomechanical loading. These bone deformities become irreversible when growth stops and are present throughout life. Adults may also present with a multitude of symptoms which include mineralisation defects, pseudo-fractures, enthesopathy and osteoarthritis (possibly due to destabilisation of the joint). Early joint replacement is common in adults with XLH. Together children and adults with XLH experience bone/joint pain, impaired mobility and reduced quality of life. Normalising FGF23 levels and thus restoring phosphate levels in children with burosumab is likely to allow normal mineralisation of newly formed bone matrix and permit normal endochondral bone formation at the growth plate. This will eliminate the typical symptoms of XLH and as the child passes through puberty and enters adulthood their bones will be fully mineralised and will have grown to their maximal potential with a normal shape and architecture. It is our assertion that skeletal health and quality of life will be improved greatly in burosumab treated XLH children. Withdrawal of burosumab in young adults is likely to result in a gradual return of osteomalacia but not rickets. When the growth plate has fused and growth has stopped the return of high FGF23 and low phosphate levels cannot result in bowed long bones and impaired mobility typical of rickets in children. This is important as it has been proposed that painful symptoms occurring in adults with XLH are caused by bone deformities and associated joint inflammation and not osteomalacia *per se* (Marie and Glorieux, 1982). The rising FGF23 and low phosphate levels will inhibit mineralisation of newly formed bone matrix in adults. This softening of the bone matrix may result in some abnormal biomechanical loading and shape changes of the lower limbs however these architectural changes will be modest in	

Consultee	Comment	Response
	comparison to the bowing observed in XLH children. As bone remodelling occurs throughout adulthood and patients with burosumab are starting their adult years with a fully mineralised bone matrix it is reasonable to assume that prior burosumab treatment will offer a longer window of improved skeletal health and life quality as the child enters adulthood.	
	This evidence regarding the long-term impact supports the modelled assumption of stabilisation of patients within health states at the end of growth. However, to address the committee's concerns regarding the long-term disease progression of patients after withdrawing burosumab, an extension of the vignette study with clinical experts has been conducted to quantify the likely long-term utility of patients over with a healed skeleton versus those with rickets at the end of growth. The five consulted clinical experts valued that the decline in quality of life of patients with severe rickets at the end of growth would be marginally greater than the decline in patients with healed rickets at baseline. The study indicates that whilst quality of life declines at a rate faster that the general population, it is not dramatically different. At the age of 40, patients that had healed rickets at the end of growth were estimated to have a utility of 0.84, compared to 0.89 in the general population. At the age of 60, patients that had healed rickets at the end of growth were estimated to have a utility of 0.69, compared to 0.82 in the general population. The quality of life predicted by the clinical expert vignette study at the age of 40 and 60 was used to update the model to more accurately predict long-term quality of life impacts of disease progression. The declines at the age of 40 and 60 were applied in addition the general population decline in quality of life (**Error! Reference source not found.**). **Figure 1. Utilities by age applied in the revised economic analysis, using declines from vignette-derived utilities at the age of 40 and 60, in addition to general population quality of life declines** **Figure not reproduced here, please see company response to ECD**	Comment noted. The committee considered 2 approaches for incorporating long-term disease progression in the economic modelling. It acknowledged that the vignette extension study was more appropriate for decision making than the alternative. The committee's conclusions relating to the long-term benefit of treatment and the modelling of disease progression can be seen in sections 4.15 and 4.22 of the FED.
	It should be noted that the clinical experts observed that it was qualitatively challenging to predict the impact of the disease on patients based on the state of their disease at the age of 18. This could be a reason for the study producing inconsistent quality of life valuations compared to additional new	Comment noted.

Consultee	Comment	Response
	data from a UK natural history study of adults with XLH. Additional data comes from an analysis of data collected as part of the RUDY database (a study of rare diseases by the University of Oxford). Mean EQ-5D values from a 2016 publication of this study were included in the submission (Forestier-Zhang *et al.*, 2016). [redacted] **Error! Reference source not found.** [redacted] This might suggest that the cost-effectiveness model overpredicts the disease progression in both arms of the model. However, the RUDY database is not limited to patients that were showing radiological evidence of rickets during growth and therefore could be milder than the population under consideration for burosumab. **Figure 1** [redacted] **Figure redacted – academic in confidence**	
Kyowa Kirin	**Revised economic analysis** As well as including the results of the Phase 3 study in the economic analysis, the updated economic analysis for burosumab includes the following amendments: • Use of ERGs preferred method of calculation of transition probabilities • Inclusion of costs of adverse events associated with burosumab, as preferred by the ERG • Amendment to age at which treatment is stopped, to reflect to	Comment noted, the committee considered the revised economic analysis and other scenarios presented by the ERG. A summary of the committee's considerations can be seen in sections 4.28 and 4.29 of the FED.

Consultee	Comment	Response
	reflect the discussion between NICE and clinical experts that took place at the committee meeting • Correction to the calculation of utilities during childhood • Incorporation of new long-term utilities in adulthood, as described above In addition to these amendments to the model that have improved the robustness of the results, particularly around the expected long-term benefit, a patient access scheme (PAS) has been provided to improve the cost-effectiveness of burosumab. The proposed PAS is of a significant magnitude that enables burosumab to remain cost-effective under a broad range of model scenarios. [redacted] Note that a discount rate of 1.5% is used as per the original company model, in line with the new data supporting the long-term outcomes in adulthood and maintaining patients to near full health. In the revised economic analysis, burosumab is associated with [redacted] undiscounted QALYs. The base case ICER is [redacted] at list price. With the PAS, the ICER is reduced to [redacted]. In a scenario analysis that attempts to quantify the impact of XLH on caregivers' quality of life, the ICER is reduced to [redacted]. Use of a 3.5% discount rate results in an ICER of [redacted] with the PAS. We believe the PAS brings the ICER well within an acceptable level, even when accounting for potential uncertainties. We are grateful to the NICE team for supporting us in expediting PASLU's review of our simple PAS submission such that it can be considered at the second committee meeting. **References not reproduced here, please see company response to ECD**	Comment noted. The committee's considerations of the appropriate discount rate can be seen in section 4.23 of the FED. See sections 4.28 and 4.29 of the FED.
British Paediatric & Adolescent Bone Group and Birmingham Women's & Children's NHS Foundation Trust (joint	1. We think the clinical evidence that is currently available and our own experiences indicates that the drug is very effective and safe with minimal side effects. We recognise that there is at present limited long term data but the provisional results of the Phase 3 Clinical Trial which compares the drug to conventional treatment are	Comment noted. Phase 3 trial evidence from CL301 was considered by the committee at the second evaluation committee meeting. A summary of the committee's considerations of the clinical evidence and results can be seen in sections 4.8, 4.12, 4.13

Consultee	Comment	Response
statement)	extremely positive in favour of Burosumab. We would recommend that the Committee do not make a decision until they have had the opportunity to review the data from the Phase 3 clinical trial. 2. We do not feel that the improvement in the quality of life for children with XLH receiving this drug has been considered. Those patients and their families who are now receiving Burosumab have commented that their life is much improved now they do not have to take medication five times a day. 3. We recognise that the cost of the drug is extremely expensive and significantly more than conventional treatment. We would hope that negotiation with the drug company could lead to a significant reduction in the cost so that it is available for all children with XLH who would benefit from treatment. 4. We recognise that there is a risk of wastage of a very expensive drug with the current ampoules that are available. We would therefore like to see the development of a multidose delivery device to reduce the risk of wastage. 5. The evaluation has not taken account of the potential reduction in costs related to the current management of XLH. This would include a reduction in the need for orthopaedic surgery to correct bowing deformities of the legs and the potential reduction in the development of dental abscesses. In addition it is likely there will an improvement in growth with this drug so that short stature as a child or adult with XLH will be reduced. There are less likely to be side effects seen with conventional therapy such as nephrocalcinosis and hyperparathyroidism.	and 4.14 of the FED. Comment noted. The committee acknowledged the inconvenient dosing regimen of conventional therapy, and noted that burosumab dosing would be more practical. See sections 4.2, 4.7 and 4.30 of the FED. Comment noted. Comment noted. Comment noted. The committee acknowledged that any reduction in the need for surgery would reduce NHS costs and represent a benefit to patients. The committee was not presented with evidence of these cost savings so it could not include this benefit in its evaluation of burosumab in a quantitative way. A summary of the committee's discussion can be seen in section 4.35 of the FED.
XLH UK	XLH UK, a charitable trust registered in England and Wales, and The XLH Network Inc., a non-profit patient advocacy group incorporated in the United States and representing patients and their families worldwide, as patient organisations for those suffering with X-Linked Hypophosphataemia, are disappointed that NICE does not currently recommend burosumab for children and young people with X-Linked Hypophosphataemia (XLH) following the recent Highly Specialised Technologies draft evaluation ID1151.	

Consultee	Comment	Response
	Burosumab offers a life-changing moment for XLH patients as it is the first and only treatment that targets the underlying mechanism of their hypophosphataemia. The trial results demonstrate strong improvements in the areas that matter most to patients, including reductions in daily pain and stiffness as well as improvements in healing of fractures and rickets severity which may limit the eventual need for repeated, invasive, corrective surgeries.	Comment noted. The committee considered the nature of XLH, and the available evidence in its evaluation of burosumab. See sections 4.1, 4.12, 4.13 and 4.14 of the FED.
	We sincerely urge NICE to reconsider their decision and make this new and truly life-changing treatment available to paediatric patients (and eventually to adults), as it can not only heal rickets in all patients, but it drastically reduces chronic pain, dental abscess risk, fatigue, and the need for surgical intervention.	Comment noted. Please seen the recommendations section (1.1) of the FED.
	While we understand that medical decisions require scientific evidence, it is already absolutely clear that treatment with burosumab is a level of magnitude better than the only other option available today (supplementation with phosphorus and calcitriol), without the potentially dangerous side-effect of kidney calcification. Paediatric patients cannot afford to wait for additional evidence, when the treatment is known to be both safe and highly effective. Any delay in access to the best available treatment—be it a matter of years, months or even weeks—reduces or even closes the window of opportunity for them to achieve the best possible health income. Children now approaching the age when bone growth ends cannot wait for additional data, since their only chance for maximising their bone growth to give them the best chance of a healthy future is right now.	Comment noted. The committee recognised there was a benefit of treatment with burosumab over current treatment options. See sections 4.3 and 4.13 of the FED.
	The NICE HST evaluating committee acknowledged that XLH is a serious condition, that childhood is the best time for treatment, and that burosumab is more effective than standard treatment, but still concluded, in essence, that the benefits of treatment were not worth the cost. Much of the consideration, however, seems based on that treatment should stop at age 18 (since burosumab is only approved for use by children in Europe), and then, as with current treatment, symptoms would recur because there is no permanent fix to the metabolic system.	Comment noted.
	This does not take into consideration the improved starting point for a	Comment noted. The committee recognised that correcting skeletal architecture in childhood could

Consultee	Comment	Response
	young-adult patient who has received burosumab treatment up to that point. We believe that if the paediatric patients' bones are properly mineralised and straightened during childhood, the progression of symptoms will at least be slowed, if not prevented completely. Properly mineralised bones are far less likely to require invasive corrective surgeries in childhood (and less likely to need additional surgeries later in life), followed by a lifetime of pain from non-unions and muscle weakness as a result of those paediatric surgeries.	provide long-term benefit. See a summary of the committee's considerations in section 4.15 of the FED.
	For children, early treatment could also potentially mean that dental abscessing may not be as prevalent (many patients report having most or all of their teeth abscessing and requiring extraction or root canals by middle age, which presents a significant economic burden). In XLH, the under-mineralised dentin creates microscopic holes leading to spontaneous dental abscessing. Treatment with phosphorus and calcitriol offers only a minimal reduction in the abscesses, presumably because the blood phosphorus levels are not stable with the old treatment. With burosumab, children will have a consistently normal serum phosphorus level while their adult teeth are forming, which should lead to proper mineralisation of the teeth and much fewer spontaneous abscesses. Visiting the local dental practice is a frustrating and emotional experience no matter what, and is worse for an XLH patient needing specialised care. It's not uncommon for a patient to find, after the root canal treatment has started, that a dentist who has never before treated an XLH patient does not have the necessary tools or expertise to complete the root canal treatment, due to the unusual shape and size of the pulp chamber and root. As a result, if it's attempted by the local dentist, there's a high chance of failure, and the crown which has cost significant money will have to be lifted and attempted once again, or the tooth may need to be extracted. In addition, locating a dental specialist for a rare disease can be time-consuming and involve substantial travel.	Comment noted. The committee acknowledged that dental abscesses cause significant pain and discomfort in children and adults. The committee noted that it was not presented with evidence relating to the effect of burosumab on dental problems. However, it understood that there was a correlation between bone symptoms and other aspects of XLH, and agreed that wider effects of XLH could be captured indirectly through RSS and RCI-G. A summary of the committee's considerations on these issues can be seen in sections 4.1 and 4.11 of the FED.
	We also believe that your report does not sufficiently acknowledge that the current treatment (phosphorus and calcitriol) is, even in the best of circumstances, far less effective in mineralising and straightening bones than burosumab is. You do say, and we completely agree, that "The clinical experts explained that it is challenging to heal bone defects with conventional therapy, and only a few people are expected to have improvements with conventional therapy, but that burosumab is expected to	Comment noted. The committee concluded that there would be long-term benefits from preventing or correcting skeletal deformities. For more information see section 4.15 of the FED.

Consultee	Comment	Response
	provide significant bone healing." Thus, it would follow that even if children are forced to go off burosumab when their bones are fully formed, they will be in far better condition at that point than they would have been if treated by phosphorus and calcitriol. Through our work with the patient community, we have heard many, many stories of patients who were on the current treatment (phosphorus and calcitriol), were advised to go off it at age 18 or thereabouts (because of the potential damage to kidneys), and then regressed over the next ten to twenty years. While that would likely still happen to some degree if burosumab is not ultimately approved for adults in Europe (as we believe it should be, since the need for phosphorus never goes away, and is in fact a major building block for not just bone but also for providing energy to muscles), at least patients who have had burosumab during their childhood will start off stronger and with straighter bones than if they'd only been treated with phosphorus and calcitriol. It should be noted too that some patients do not respond well to phosphorus/calcitriol, and other patients cannot tolerate the supplements. Phosphorus supplements in the quantity needed for clinical benefit cause most people extreme gastrointestinal distress, and patients who report this say it as people who have lived with chronic bone pain for their entire life. Some will even experience severe gastrointestinal pain from phosphorus supplements before they reach a clinically-effective level, which means that these patients cannot be on the current phosphorus/calcitriol treatment, so their only options are no treatment or burosumab. We also believe you do not fully comprehend the nature and extent of pain experienced by XLH patients, even when they are on the current treatment (phosphorus and calcitriol). The XLH community is, I would say, not so easily fazed by pain since the disorder affects patients from birth, and consequently growing up with the chronic bone pain and aches increases their pain tolerance. Pain is simply "normal" for XLH patients, and is largely disregarded until it becomes extreme. We do not believe that this is adequately documented in the draft evaluation from NICE. Bone pain is significant in the life of a patient with XLH, since patients are frequently taking pain medication over long periods of time, and even so, some need to take time away from school, work or social activities. This pain, coupled with	Comment noted. The committee understood that many people who stop treatment would start again when symptoms return (FED section 4.5). However, the committee concluded that there would be long-term benefits from preventing or correcting skeletal deformities. For more information see section 4.15 of the FED. Comment noted. The committee The committee recognised that conventional therapy can cause unpleasant side effects, and that only a small proportion of people are expected to have improvements with conventional therapy. See sections 4.2 and 4.7 of the FED. Comment noted. The committee acknowledged that children and adults with XLH will suffer from lifelong disability and pain. It also recognised that people with XLH would have significant muscle weakness and fatigue. See sections 2.2 and 4.1 of the FED.

Consultee	Comment	Response
	the chronic fatigue from low serum phosphorus that patients experience, makes living with XLH a particularly relentless and stressful experience that can lead to further physiological and emotional issues that will require treatment. Pain and fatigue tend to multiply each other, so a patient who is in pain, but not fatigued, can often push through the pain. A person with both pain and fatigue, however, does not have the energy to push on. The fatigue can also magnify a lower level of pain, depleting the energy needed to cope with the pain, and setting in motion a vicious cycle of ever-increasing pain and ever-reduced ability to cope. And patients with XLH, by virtue of the phosphorus-wasting, have both pain and fatigue built into their lives.	
	The report refers to burosumab as having short-term clinical benefits. We believe you meant in terms of the metabolism going back to its old phosphate-wasting ways once the burosumab is out of the system. That is not the only way of looking at the benefits however. It's pretty clear that burosumab does a better job of mineralising and straightening the bone that the current phosphorus/calcitriol treatment does, and that benefit will last, if not for a lifetime, at least decades, putting the patient in a better health state before going off burosumab.	Comment noted. The committee acknowledged that there would be long-term benefits from preventing or correcting skeletal deformities. For more information see section 4.15 of the FED.
	We believe the patients who could be on burosumab as children will have optimum serum phosphorus levels over long periods of time (unlike the phosphorus/calcitriol supplements that rise and fall every few hours) ensuring quality mineralised bone and nice straight legs, arms and spines, all the way to the point of adolescence whereby their skeleton has stopped growing, their optimum height reached, and the bones as straight as possible. This could mean that those children will not require the copious amounts of limb reconstructive surgery since their legs will be already straight and their levels of bone deterioration will be less significant than if they were already bowed and deformed before going back to a state of chronic phosphorus deprivation. At the very least, bones that meet at joints at correct angles after burosumab treatment in childhood will be less prone to early-onset osteoarthritis.	Comment noted. The committee recognised that treatment could reduce the need for surgical intervention, which it agreed represented a significant benefit for people with XLH. See section 4.35 of the FED.
	We also do not believe that the evaluation has considered the impact of past injuries on a patient's well-being, along with the fear of future injuries or re-	Comment noted. The committee recognised that painful symptoms could result from surgery. See

Consultee	Comment	Response
	injury. Once children have had corrective limb surgery, they are forever weakened in the relevant portion of bone by the procedure. To make things worse, because of the very nature of XLH, which means not being able to mineralise quality bone, the orthopaedic fractures may take far more time to heal (years, rather than weeks), and may not heal well in the end, if it heals at all. With that in mind, returning to a productive life after surgery is yet another challenging experience. We have heard from a number of both children and adults who have injured themselves and have a fear of further injuring themselves, even sometimes suffering from compound fractures, because of a limb weakened in the course of orthopaedic surgery.	section 4.1 of the FED.
	We also believe that this evaluation does not consider the mental and emotional health of paediatric patients with XLH. We cannot overstate the significance of a treatment that allows these young patients to experience a childhood more similar to that of their peers. Caregivers of paediatric patients in clinical trials have reported significant increases in their children's physical and emotional wellbeing.	Comment noted. The emotional burden of XLH was considered by committee and is summarised in section 4.7 of the FED.
	In terms of the economic value of burosumab, we will be the first to admit we are not an economists. We do think, however, that you underestimate, again, the benefit of being on the best possible treatment during childhood, as compared to the really quite inadequate current treatment (phosphorus and calcitriol). You reject one aspect of the proposed economic model, which was that "nearly all people having burosumab [would be] in the healed health state by the time treatment was stopped, whereas there [would be] a distribution of people across the different health states for conventional therapy." While we understand the full evidence for this has not yet been presented, simply because no one has been on burosumab for an entire childhood, it's quite clear, based on the better bone healing/straightening on burosumab that has already been shown to occur almost immediately upon beginning burosumab treatment, that this is going to be true. Additionally, we believe you're conflating two issues in this discussion. One is the degree to which conventional treatment gets a patient to a "fully healed" state of good health, and the other is whether they'll STAY that way after stopping burosumab. It's pretty clear that for patients on the current	Comment noted. The committee considered the direct treatment benefit and wider benefit of burosumab in its evaluation of burosumab. It took into account the effects of burosumab and conventional therapies on the condition during childhood (see section 4.18), and then discussed the long-term predictions for what would happen in adulthood (see sections 4.20–4.22). The committee recognised that people treatment with burosumab will have a better starting point when they reach adulthood, compared with those on conventional therapy. See section 4.15 of the FED.

Consultee	Comment	Response
	phosphorus/calcitriol treatment, they NEVER get to a fully healed state. Not one of them. That needs to be compared to the logical conclusion that can be made even with current evidence, that the vast majority of burosumab patients will reach a fully healed state by the end of adolescence compared to NONE on conventional treatment. Sure, both groups will revert to phosphate-wasting if taken off treatment. But one will have a better starting point, delaying the deterioration.	
	We also believe you are underestimating the cost of both surgery and disability in adults with XLH, and how much could be saved by giving patients a stronger foundation during childhood. Through our work with the patient community, we're aware of the many, many patients who have had double-digits' worth of surgeries by the time they're forty! Operations done during childhood later have to be repaired or replaced or the limb must be reconstructed once again in thirties and forties. Others have knee and hip surgeries in their thirties and forties, far earlier than the general population. Patients develop spinal stenosis and spinal calcifications, requiring multiple operations in their 50s and 60s, again, far earlier than the general population.	Comment noted. The committee recognised that there would be cost savings and benefits from avoiding surgery, and agreed that this was relevant to consider. The committee was not presented with evidence of these cost savings so it could not include this benefit in its evaluation of burosumab in a quantitative way. A summary of the committee's discussion can be seen in section 4.35 of the FED.
	Adults with XLH often find it hard to complete a full day of work, due to persistent pain, chronic fatigue, and mobility restrictions. Through our work with the patient community, we've heard countless stories of heartbroken patients who loved their work—as nurses, teachers, and other highly rewarding careers—but were forced to retire or go on disability living allowances a decade or more before they would have liked to stop. Or they've been dissuaded completely from a career they're passionate about, because of the physical toll it would have wrought on their weakened musculoskeletal system. That has a significant financial impact on both the patient and society in general. And these are not people who complain at the least little thing or are looking for an excuse to stay home. These are patients who are unfazed by broken bones, often untreated, and who STILL go to work or raise families or are otherwise productive members of society until it just becomes too much for them.	Comment noted. The committee understood that there XLH had a significant impact on people's physical health, which affected their working choices and finances. See sections 2.2, 4.1 and 4.30 of the FED.
	On behalf of the patients and carers of patients with XLH, we ask that NICE, NHS England, and all stakeholders work together and work quickly to find a way to ensure patients will receive access in a timely manner to burosumab,	Comment noted.

Consultee	Comment	Response
	a life-changing treatment that will have a substantial positive impact on the patients' ability to participate in everyday activities over a lifetime, and the quality of life for both the patients and their families. Children and young people currently living with XLH are running out of time to have a reasonably good, healthy future.	
Metabolic Support UK	**Metabolic Support UK response to draft guidance on burosumab for treating X-linked hypophosphataemia (ID1151)** Metabolic Support UK, as the umbrella patient organisation for Inherited Metabolic Disorders, is disappointed that NICE does not recommend re-imbursement of the treatment burosumab for X-linked Hypophosphatemia (XLH) in children and young people following the recent Highly Specialised Technologies evaluation. Burosumab is the first and only treatment to target the underlying pathophysiology of XLH. An injection given every two weeks from the age of one until the skeleton stops growing, aims to increase reabsorption of phosphate from the kidney and, through vitamin D production, improve intestinal absorption of calcium and phosphate. Metabolic Support UK has seen the positive impact on XLH patients who have received the treatment under the clinical trials and early access scheme. Parents of children that have benefitted from the treatment report strong improvements in adherence to the treatment pathway, physical functioning, mobility, bone density and straightening, pain levels and social inclusion; overall impacting on the quality of life and mental wellbeing not just for the patient but their parents/carers and wider family. Clinical experts stated, during the Committee meeting, the clear benefits of the treatment for all children affected by XLH and that early treatment would reduce the need for surgical intervention and avoidable suffering. While we are pleased that the Committee recognises the meaningful clinical benefits of burosumab and the lasting effect over the patient's lifetime, due to the prevention of irreversible bone damage, we do not feel that the long-term benefits when patients reach adulthood have been fully considered. Though the marketing authorisation for burosumab does not include adults, early access to, and adherence of, this treatment during the pivotal bone growth years could bring substantial benefits post-adolescence. We believe the Committee's conclusion stated in 4.13 'burosumab would not	Comment noted. Comment noted. The committee acknowledged that burosumab was the first treatment affecting the pathophysiology of XLH. See section 4.34 of the FED. Comment noted. Comment noted. The committee acknowledged that there would be long-term benefits from preventing or correcting skeletal deformities. For more information see section 4.15 of the FED.

Consultee	Comment	Response
	improve other aspects of XLH in the long-term' does not address the fact that fixing or correcting skeletal deformities during childhood will see the improvements continue into adulthood. Adult patients successfully treated as children will see an improvement in the lifelong disability, a reduced need for corrective surgery and experience less debilitating pain and mobility issues. The social and psychological benefits seen by patients on the clinical trial as a result of the physical improvements will also continue into adulthood, reducing the burden of care in the long-term. Metabolic Support UK has engaged and endeavoured to bring the patient voice and experience into the process where possible. The data and evidence in this area is limited, in common with all products considered under the current Highly Specialised Technology appraisal process. We hope that NICE, NHS England and all stakeholders can work together to agree a way to ensure patients will receive access to this important treatment that would have a substantial impact on quality of life and ability to participate in everyday activities over a lifetime. Yours sincerely Joanne Taylor Acting Chief Executive, Metabolic Support UK	Comment noted.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Royal Manchester Children's Hospital	**Has all of the relevant evidence been taken into account?** In my opinion, all the documents that were presented at the 1st evaluation held on 23rd May 2018 were considered. I hope that Kyowa Kirin will present data from the Burosumab Phase III trial for consideration at next evaluation meeting to be held on 25th July 2018. **Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?** The trial data suggests that Burosumab is effective in healing rickets and improving muscle function & linear growth in children with X-linked Hypophosphataemia. My patients with X-linked Hypophosphataemia have	Comment noted. The committee considered evidence from the phase 3 trial (CL301) presented by the company at the second evaluation committee meeting. Comment noted. The committee recognised that there is a treatment benefit associated with burosumab, see FED sections 4.12, 4.13 and 4.14.

Nominating organisation	Comment	Response
	participated in Burosumab Phase II & III trials at Royal Manchester Children's Hospital. These patients were receiving treatment with inorganic phosphate 4 to 5 times a day and Alfacalcidol once a day administered orally, prior to participating in Burosumab trials. I have observed dramatic healing of rickets in these patients. So there is no doubt that treatment with Burosumab is superior to conventional therapy in healing rickets. However, the current cost of Burosumab is quite expensive for treating a non-fatal condition. **Are the provisional recommendations sound and a suitable basis for guidance to NHS England?** YES, but I sincerely hope that Kyowa Kirin will consider significantly reducing the cost of Burosumab, so that this medication can be used to treat children & adolescents with X-linked Hypophosphataemia.	Comment noted.

Comments received from commentators

No comments received.

Summary of comments received from members of the public

Theme	Response
XLH causes pain and fatigue which impacts schooling and work	Comment noted. The committee understood the nature of XLH, and recognised that it can cause severe symptoms and affect people's ability to participate in educational and social activities and complete usual activities. See sections 4.1, 4.2 and 4.30 of the FED.
There is a psychological impact of XLH on children, adults and families	Comment noted. The committee understood that XLH has a psychological and emotional impact on patients and their families. See sections 4.1 and 4.7 of the FED.
Conventional therapy is impractical, unpleasant and ineffective	Comment noted. The committee acknowledged that there were a number of limitations associated with conventional therapy, including impractical dosing regimens, an unpleasant taste, significant side effects and limited effectiveness. See sections 4.2, 4.5 and 4.7 of the FED.

Theme	Response
Corrective surgical intervention has a broad impact	Comment noted. The committee recognised that surgical intervention was distressing, disruptive and costly. It noted that these benefits were not captured in the economic model, but if they were it would improve the cost effectiveness of burosumab. See sections 4.1, 4.2, 4.15 and 4.35 of the FED.
Burosumab is more effective than current treatment options	Comment noted. The committee considered the evidence from clinical trials and information from the experts present at the evaluation committee meeting and from stakeholders. It agreed that the evidence suggested that burosumab was more effective than conventional therapy. See sections 4.13 and 4.14 of the FED.
Improvements in bone deformity will be long-term	Comment noted. The committee recognised that there would be important long-term benefits from correcting or preventing skeletal deformities in childhood. See section 4.15 of the FED.
Burosumab should be considered in adults as well as children	Comment noted. The marketing authorisation for burosumab does not include adults. Therefore the committee could not consider the use of burosumab in adults. See sections 4.6 and 4.7 of the FED.

The following consultees/commentators indicated that they had no comments on the Evaluation Consultation Document:

Department of Health and Social Care

NHS England

Highly Specialised Technology Evaluation

X-Linked Hypophosphataemia – burosumab [ID 1151]

Manufacturer's Response to the Evaluation Consultation Document (ECD)

Kyowa Kirin are grateful for the opportunity to provide additional evidence to address the uncertainties the committee noted in the ECD. In the ECD, having considered the view of patients and clinical experts, the committee concluded that burosumab has the potential to significantly improve patients' quality of life in the long term by modifying the disease during childhood. In this response, we provide:

- The results of the recently reported Phase 3 study comparing burosumab with conventional therapy (CL301) (Appendix A)
- Evidence supporting the likely long-term disease progression during adulthood
- An updated economic analysis including a patient access scheme that improves the cost-effectiveness of burosumab (Appendix B).

Phase 3 study results

The Phase 3 study addresses concerns around the clinical evidence presented in the original submission, which consisted only of single arm studies (CL201 and CL205) and historical controls (for CL201 only). CL301 was a Phase 3 randomised, controlled study in patients aged 1 to 12 years, comparing burosumab to conventional therapy, which is the UK current standard of care. This evidence significantly reduces the uncertainty around the clinical effectiveness of burosumab in children aged 1 to 12 years, and demonstrated that burosumab is significantly more efficacious than conventional therapy.

Clinical experts were clear during the committee meeting that they believed burosumab would be at least as efficacious, if not more so, in patients aged 13-17, because this is the age of the greatest skeletal growth. Whilst we acknowledge that RCT evidence is not available within this age range, we believe the ECD fails to acknowledge both the unmet need and the clinical experts' expectations for this age group.

The ECD incorrectly states that only children with a Rickets Severity Score (RSS) of 1.5 or above were included in the CL201 and CL205 studies. We would like to clarify that the Phase 2 studies for burosumab included paediatric patients across a wide spectrum of disease severity including those with less severe rickets (RSS total score ranged from 0.0 to 4.5 in CL201 and from 1.0 to 6.5 in CL205). The CL301 study enrolled subjects with an RSS of 2.0 or greater, to best demonstrate a treatment effect and maximise the ability to detect change, as recognised within the ECD. This has implications for the economic analysis since incorporating evidence for only those with an RSS>2.0 would not enable a full simulation of

the long-term impact. Consequently, the results of the CL301 study have been included within the economic analysis by combining all the Phase 2 and 3 study data for burosumab, as well as utilising the UK chart-review data and the Phase 3 control arm for the conventional therapy arm. Incorporating this additional data significantly reduces the uncertainty around the cost-effectiveness.

Expected long-term outcomes during adulthood

During the committee meeting, clinical experts explained that even if bone defects are corrected in childhood, people will continue to have symptoms and be at risk of new bone defects into adulthood. The ECD states that the committee understood this to mean that burosumab would not affect the progression of bone manifestations of XLH during adulthood (for example, increased risk of osteomalacia and accompanying stress fractures and pain) or other ongoing aspects of the condition such as metabolic effects of low phosphate (for example, muscle weakness and fatigue). As a consequence, the committee concluded there would be long term benefits from fixing or preventing childhood skeletal deformities, but that burosumab would not affect other aspects of XLH in the long term. We would accept that, following discontinuation of burosumab, adults would over time experience ongoing aspects of XLH such as metabolic effects of low phosphate. However, we would like to further illustrate the broader impact of fixing or preventing childhood skeletal deformities on life-long quality of life, compared to ongoing aspects of disease in adulthood, such as oeteomalacia.

As noted by one of the patient representatives at the first committee meeting, the detriments in adult quality of life are very much associated with deformities. The uncertainty highlighted by the committee is the effect of osteomalacia on quality of life in the absence of such previous deformities. Painful symptoms occurring in adults with XLH are caused by bone deformities and associated joint inflammation and not osteomalacia *per se* (Marie and Glorieux, 1982). A study – co-authored by Glorieux, one of the leading authorities on metabolic bone disorders – showed that, despite the absence of symptoms in some adult XLH patients, they still have active bone disease characterised by moderate to severe osteomalacia. In addition, bone pain and associated symptoms in osteomalacia usually result from decreased calcified bone volume. In patients with XLH, decreased calcified bone volume is not detected despite the presence of moderate to severe osteomalacia (Marie and Glorieux, 1982).

Avoiding or correcting skeletal deformities is expected to result in reduced osteoarthritis, stiffness and enthesopathy, and consequently reduced pain and improved mobility throughout their lifetime. Nearly half of adults have undergone some form of corrective surgery of skeletal abnormalities that originated during skeletal growth (Chesher *et al.*, 2018). It is therefore expected that the need for corrective surgery will be much reduced or avoided, and that operations that may be required later in life (e.g. arthroplasties) would also be delayed or avoided. It is expected that this type of surgery will be greatly reduced or will no longer be required if the patient received burosumab in childhood.

Bone remodelling continues throughout life. In patients with XLH this means that new bone being laid down may not be fully mineralised, leading to a reduction in bone quality. The clinical effects of this gradual reduction of bone quality in adult life will not become apparent until it

reaches a clinically meaningful threshold. Patients with XLH who have had no previous disease-modifying treatment can be expected to reach adulthood with significantly reduced bone quality as a result of suboptimal phosphate control and will therefore reach any such threshold earlier than patients who have had such treatment. Therefore, in a cohort of adults managed with standard of care it would be expected that, relative to those treated with burosumab, they would start adulthood with much lower bone quality, in addition to any skeletal deformities present from childhood. These expectations were agreed in consultation with Prof Colin Farquharson, an expert in skeletal biology (Box 1). Taken together, progression of symptoms and associated decline quality of life following discontinuation of burosumab is expected to be more delayed than current treatment.

Box 1. Scientific statement from Prof Colin Farquharson, Professor of Skeletal Biology

The progression of X-linked hypophosphatemic rickets (XLH) in children leads to muscle weakness, short stature, lower limb deformities and poorly mineralised bone. The primary cause of the skeletal defects is defective mineralisation of newly formed bone matrix (osteoidosis). Poor mineralisation is caused by elevated circulating levels of FGF23 which drives excessive phosphate excretion resulting in low phosphate levels. In the growing child impaired mineralisation occurs at all bone forming surfaces (osteomalacia) including the chondro-osseous junction at growth plate which results in stunted and abnormal growth of the long bones (endochondral ossification). This in turn leads to lower-extremity bowing, altered gait and abnormal biomechanical loading. These bone deformities become irreversible when growth stops and are present throughout life. Adults may also present with a multitude of symptoms which include mineralisation defects, pseudo-fractures, enthesopathy and osteoarthritis (possibly due to destabilisation of the joint). Early joint replacement is common in adults with XLH. Together children and adults with XLH experience bone/joint pain, impaired mobility and reduced quality of life.

Normalising FGF23 levels and thus restoring phosphate levels in children with burosumab is likely to allow normal mineralisation of newly formed bone matrix and permit normal endochondral bone formation at the growth plate. This will eliminate the typical symptoms of XLH and as the child passes through puberty and enters adulthood their bones will be fully mineralised and will have grown to their maximal potential with a normal shape and architecture. It is our assertion that skeletal health and quality of life will be improved greatly in burosumab treated XLH children.

Withdrawal of burosumab in young adults is likely to result in a gradual return of osteomalacia but not rickets. When the growth plate has fused and growth has stopped the return of high FGF23 and low phosphate levels cannot result in bowed long bones and impaired mobility typical of rickets in children. This is important as it has been proposed that painful symptoms occurring in adults with XLH are caused by bone deformities and associated joint inflammation and not osteomalacia *per se* (Marie and Glorieux, 1982).

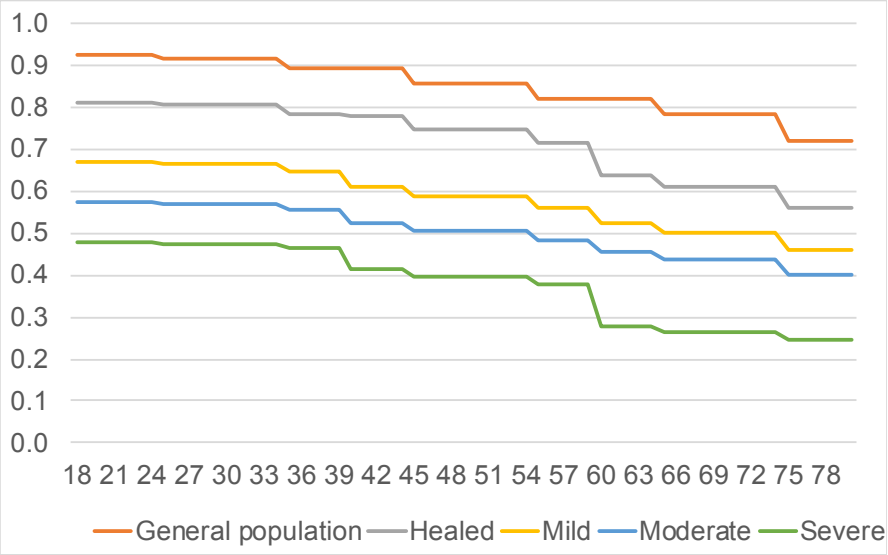
The rising FGF23 and low phosphate levels will inhibit mineralisation of newly formed bone matrix in adults. This softening of the bone matrix may result in some abnormal biomechanical loading and shape changes of the lower limbs however these architectural changes will be

modest in comparison to the bowing observed in XLH children. As bone remodelling occurs throughout adulthood and patients with burosumab are starting their adult years with a fully mineralised bone matrix it is reasonable to assume that prior burosumab treatment will offer a longer window of improved skeletal health and life quality as the child enters adulthood.

This evidence regarding the long-term impact supports the modelled assumption of stabilisation of patients within health states at the end of growth. However, to address the committee's concerns regarding the long-term disease progression of patients after withdrawing burosumab, an extension of the vignette study with clinical experts has been conducted to quantify the likely long-term utility of patients over with a healed skeleton versus those with rickets at the end of growth.

The five consulted clinical experts valued that the decline in quality of life of patients with severe rickets at the end of growth would be marginally greater than the decline in patients with healed rickets at baseline. The study indicates that whilst quality of life declines at a rate faster that the general population, it is not dramatically different. At the age of 40, patients that had healed rickets at the end of growth were estimated to have a utility of 0.84, compared to 0.89 in the general population. At the age of 60, patients that had healed rickets at the end of growth were estimated to have a utility of 0.69, compared to 0.82 in the general population. The quality of life predicted by the clinical expert vignette study at the age of 40 and 60 was used to update the model to more accurately predict long-term quality of life impacts of disease progression. The declines at the age of 40 and 60 were applied in addition the general population decline in quality of life (Figure 1).

Figure 1. Utilities by age applied in the revised economic analysis, using declines from vignette-derived utilities at the age of 40 and 60, in addition to general population quality of life declines



It should be noted that the clinical experts observed that it was qualitatively challenging to predict the impact of the disease on patients based on the state of their disease at the age of 18. This could be a reason for the study producing inconsistent quality of life valuations compared to additional new data from a UK natural history study of adults with XLH.

Additional data comes from an analysis of data collected as part of the RUDY database (a study of rare diseases by the University of Oxford). Mean EQ-5D values from a 2016 publication of this study were included in the submission (Forestier-Zhang *et al.*, 2016). [redacted] This might suggest that the cost-effectiveness model overpredicts the disease progression in both arms of the model. However, the RUDY database is not limited to patients that were showing radiological evidence of rickets during growth and therefore could be milder than the population under consideration for burosumab.

Figure 2. Correlation of EQ-5D-5L baseline utility scores and age from XLH patients in RUDY (n=40)

Revised economic analysis

As well as including the results of the Phase 3 study in the economic analysis, the updated economic analysis for burosumab includes the following amendments:

- Use of ERGs preferred method of calculation of transition probabilities
- Inclusion of costs of adverse events associated with burosumab, as preferred by the ERG
- Amendment to age at which treatment is stopped, to reflect to reflect the discussion between NICE and clinical experts that took place at the committee meeting
- Correction to the calculation of utilities during childhood
- Incorporation of new long-term utilities in adulthood, as described above

In addition to these amendments to the model that have improved the robustness of the results, particularly around the expected long-term benefit, a patient access scheme (PAS) has been provided to improve the cost-effectiveness of burosumab. The proposed PAS is of a significant magnitude that enables burosumab to remain cost-effective under a broad range of model scenarios. [redacted]

Note that a discount rate of 1.5% is used as per the original company model, in line with the new data supporting the long-term outcomes in adulthood and maintaining patients to near full health. In the revised economic analysis, burosumab is associated with [redacted] undiscounted QALYs. The base case ICER is [redacted] at list price. With the PAS, the ICER is reduced to [redacted]. In a scenario analysis that attempts to quantify the impact of XLH on caregivers' quality of life, the ICER is reduced to [redacted]. Use of a 3.5% discount rate results in an ICER of [redacted] with the PAS.

We believe the PAS brings the ICER well within an acceptable level, even when accounting for potential uncertainties. We are grateful to the NICE team for supporting us in expediting PASLU's review of our simple PAS submission such that it can be considered at the second committee meeting.

References

Chesher, D. *et al.* (2018) 'Outcome of adult patients with X-linked hypophosphatemia caused by PHEX gene mutations (accepted for publication)', *Journal of Inherited Metabolic Disease*.

Forestier-Zhang, L. *et al.* (2016) 'Health-related quality of life and a cost-utility simulation of adults in the UK with osteogenesis imperfecta, X-linked hypophosphatemia and fibrous dysplasia.', *Orphanet journal of rare diseases*, 11(1), p. 160. doi: 10.1186/s13023-016-0538-4.

Marie, P. J. and Glorieux, F. H. (1982) 'Bone histomorphometry in asymptomatic adults with hereditary hypophosphatemic vitamin D-resistant osteomalacia', *Metabolic Bone Disease and Related Research*, 4(4), pp. 249–253. doi: 10.1016/0221-8747(82)90035-2.

Appendix A: Study UX023-301 – 40 week analysis

Summary

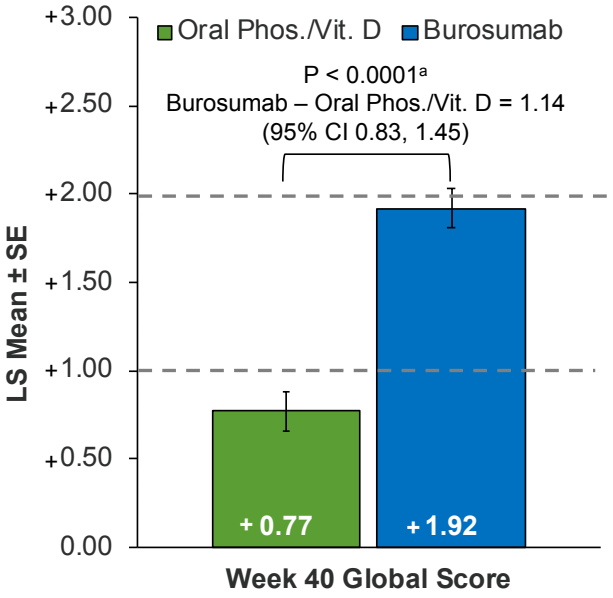
Recently available data from UX023-CL301 (CL301) addresses two key concerns of the NICE committee:

1) **ECD Section 4.7: The committee recognised that the lack of randomised controlled trial data substantially reduced the robustness of the clinical-effectiveness comparison, and that the ongoing randomised control trial (CL301) would provide more robust data.**

CL301 is a multicentre, randomised, open-label, Phase 3 study comparing the efficacy and safety of burosumab with active control (oral phosphate/active vitamin D therapy) in children with clinical evidence consistent with XLH (aged 1 to ≤12 years).

Compared to conventional therapy, treatment with burosumab for 40 weeks significantly improved rickets severity and lower limb deformity compared to conventional therapy as shown by greater increases in RGI-C (Figure 1), greater decreases in RSS scores, and greater decreases in ALP. Substantial healing (RGI-C >= +2.0) was observed in 72.4% of patients receiving burosumab compared to 6.3% of patients receiving conventional therapy (p<0.0001). Burosumab significantly improved phosphate metabolism as shown by a greater increase in serum phosphorus and TmP/GFR compared to conventional therapy.

Figure 1. RGI-C Global Scores and Responders at Week 40 (Full Analysis Set)



Week 40 Responders[b] (RGI-C ≥+2.0), n (%)

Oral Phos./Vit. D (N=32)	Burosumab (N=29)
2 (6.3%)	21 (72.4%)
Odds Ratio burosumab vs. oral phos./vit. D: 39.139 95% CI: 7.238, 211.656	
P < 0.0001	

[a] ANCOVA model includes treatment and baseline age stratification as factors and baseline RSS as a covariate.
[b] Logistic regression model includes treatment and baseline age stratification as factors and baseline RSS as a covariate
RGI-C 7-point ordinal scale: +3=complete healing, +2=substantial healing, +1=minimal healing, 0=unchanged, -1=minimal worsening, -2=moderate worsening, 3=severe worsening

The magnitude of the treatment effect, in terms of reducing the severity of rickets, was similar to that observed in the Phase 2 study (CL201). In patients treated with burosumab Q2W for 40 weeks in CL201 and CL301, respectively:

- The RGI-C global scores were +1.72 and +1. 92 at 40 weeks, compared to baseline.

- The proportion of patients with substantial healing (RGI-C global score ≥+2.0) was 69.2% and 72.4%.
- The reduction in RSS total score from baseline was 61% and 64%.

Burosumab was also associated with strong trends in improvement in growth (as shown by increasing the growth velocity Z score to within normal range) and physical functioning (as shown by increases in distance walked in the 6MWT).

The safety profile of burosumab in this phase 3 study was similar to that of the previous phase 2 clinical trials in paediatric patients. Four serious adverse events occurred (three with burosumab); all were deemed not related to study drug. There were no deaths or discontinuations (Ultragenyx Press Release, 2018). [redacted]. In addition, there were no concerns regarding bone mineralisation parameters or imaging studies (serum phosphorus, serum calcium and serum intact parathyroid hormone or renal ultrasounds) (Ultragenyx Press Release, 2018).

2) **ECD Section 4.7: The committee noted that the company did not provide comparative evidence for children aged 1 to 4 years, and agreed a robust assessment of clinical effectiveness in this group would be challenging. It concluded that the presented evidence was limited, and agreed that there would be uncertainty in its assessment of clinical effectiveness.**

CL301 included patients aged 1-4 years old. In a pre-specified subgroup analysis, the improvement in the RGI-C and RSS scores observed with burosumab compared to conventional therapy [redacted]. Although the results should be interpreted with some caution due to the small sample size, this indicates that burosumab is [redacted].

Methodology

UX023-CL301 is a multicentre, randomised, open-label, Phase 3 study comparing the efficacy and safety of burosumab with active control (oral phosphate/active vitamin D therapy) in children with clinical evidence consistent with XLH (aged 1 to ≤12 years), including demonstrated hypophosphatemia, radiographic evidence of rickets (≥ 2.0 points RSS total score), and PHEX mutation or variants of uncertain significance (Ultragenyx, CL301 Protocol, 2016). The study methodology is summarised in Table 1.

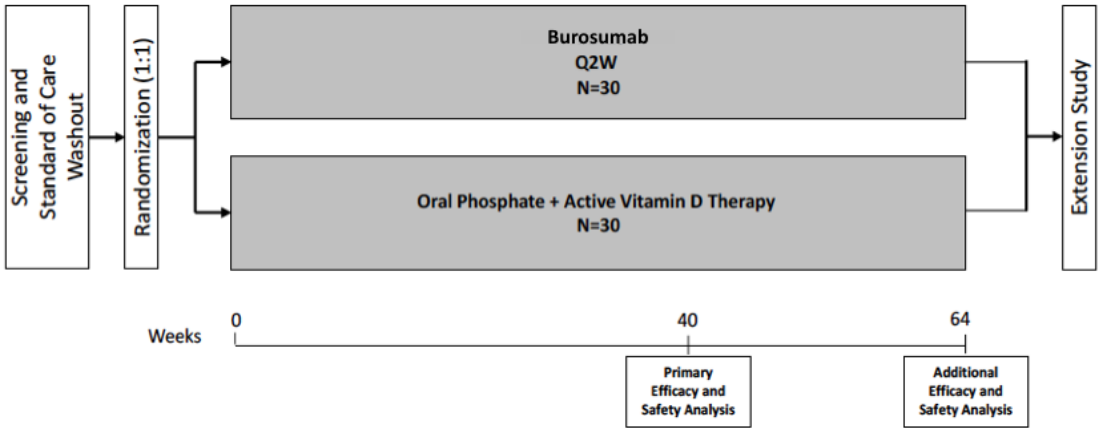
Patients were randomised 1:1 to receive open-label burosumab administered by subcutaneous injection or oral phosphate and active vitamin D therapy (conventional therapy) for a total of 64 weeks (Figure 2). Randomisation was stratified by baseline rickets severity (RSS total score ≤2.5 vs >2.5) and age (<5 vs ≥5) as well as by region (Japan vs rest of the world).

Patients assigned to the burosumab treatment group received burosumab at a starting dose of 0.8 mg/kg every two weeks (Q2W). The dose may be increased to 1.2 mg/kg at any time during the study if a subject meets the following dose-adjustment criteria: 1) two consecutive serum phosphorus measurements are below the normal range; 2) serum phosphorus has increased by < 0.5 mg/dL from baseline; and 3) the subject has not missed a dose of study drug that would account for the decrease in serum phosphorus. Patients randomised to burosumab are to remain off of oral phosphate/active vitamin D therapy throughout the duration of the study. Because of the variability in the doses and dosing frequencies of oral phosphates and active vitamin D therapies in clinical practice, these treatments are individualised for each subject at the investigator's discretion.

As in previous phase 2 studies, rickets severity was assessed using two complementary measures, the RGI-C and the RSS.

The primary analysis (presented here) was at Week 40; analyses at Week 64 will assess the durability of treatment effect, additional efficacy outcomes, and long term safety. Patients from either treatment groups who complete the active-controlled treatment period of the study (64 weeks) may be eligible for an extension study and receive burosumab treatment for up to an additional 96 weeks or until the study drug is commercially available.

Figure 2. Overall study design



Source: UX023-CL301 Protocol, Figure 2.1.

Table 1. Summary of methodology for CL301

Study name	**UX023-CL301**
Objectives	Evaluate the effects of burosumab on improving rickets, maximising growth, and restoring phosphorus homeostasis compared with active control (oral phosphate/active vitamin D therapy), as well as to evaluate the safety of burosumab, in children with XLH (aged 1 to ≤ 12 years) with confirmed evidence of rickets.
Location	The study enrolled patients across [redacted]
Design	Multicentre, randomised, open-label, Phase 3 study
Duration of study	64 weeks: • Primary analysis is at Week 40 • Analyses at Week 64 will assess the durability of treatment effect, additional efficacy outcomes, and long term safety • Patients from either treatment groups who complete the active-controlled treatment period of the study (64 weeks) may be eligible for an extension study and receive burosumab treatment for up to an additional 96 weeks or until the study drug is commercially available.
Sample size	n = 61
Main inclusion criteria	• Male or female, aged 1 to ≤12 years with radiographic evidence of rickets with a minimum rickets severity score (RSS) total score of 2 as determined by central read • PHEX mutation or variant of uncertain significance in either the patient or in a directly related family member with appropriate X-linked inheritance • Biochemical findings associated with XLH: Serum phosphorus <3.0 mg/dL (0.97 mmol/L) 4) Serum creatinine within age-adjusted normal range*

	• Serum 25(OH)D above the lower limit of normal (≥16 ng/mL) at the Screening Visit • Have received both oral phosphate and active vitamin D therapy for ≥ 12 consecutive months (for children ≥3 years of age) or ≥ 6 consecutive months (for children <3 years of age) prior to the Screening Visit
Main exclusion criteria	• Tanner stage 4 or higher through physical examination • Height percentile >50% based on country-specific norms • Use of aluminium hydroxide antacids, systemic corticosteroids, acetazolamide, and thiazides within 7 days prior to the Screening Visit • Current or prior use of leuprorelin, triptorelin, goserelin, or other drugs known to delay puberty • Use of growth hormone therapy within 12 months before the Screening Visit • Presence of nephrocalcinosis on renal ultrasound grade 4 based on the following scale: o 0 = Normal o 1 = Faint hyperechogenic rim around the medullary pyramids o 2 = More intense echogenic rim with echoes faintly filling the entire pyramid o 3 = Uniformly intense echoes throughout the pyramid o 4 = Stone formation: solitary focus of echoes at the tip of the pyramid • Planned or recommended orthopaedic surgery (implantation or removal), including staples, 8-plates or osteotomy, within first 40 weeks of the study • Hypocalcaemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits • Evidence of hyperparathyroidism • Use of medication to suppress PTH (e.g., cinacalcet, calcimimetics) within 2 months prior to the Screening Visit • Use of any investigational product or investigational medical device within 30 days (within 4 months in Japan) prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments
Method of randomisation	Subjects were randomised 1:1 to receive open-label burosumab by subcutaneous injection or active control via an Interactive Web Response System (IWRS) based on a randomisation schedule developed by an independent third-party vendor. Randomisation was stratified by baseline rickets severity (RSS total score ≤2.5 vs >2.5) and age (<5 vs ≥5) as well as by region (Japan vs rest of the world).
Method of blinding	Blinding was not applied in the study. An open-label study design was chosen since blinding such a study would be problematic due to the different methods of administration and the individualised nature and frequent dose adjustments needed with oral phosphate/active vitamin D therapy.
Intervention(s) (n =) and comparator(s) (n =)	• Open-label burosumab by subcutaneous injection (n = 29) • Oral Phosphate/Active Vitamin D (conventional therapy) - Active control (n = 32)
Baseline differences	Demographic and baseline characteristics were similar across the treatment groups (Table 3). Patients in the conventional therapy arm had received prior conventional therapy for [redacted] patients in the burosumab arm; they were [redacted] and had started conventional therapy [redacted].
Duration of follow-up, lost to follow-up information	All subjects completed at least 40 weeks on study (primary analysis). A number of subjects have continued the study up to week 64 (results not yet available).

Statistical tests	The full analysis set (used for both efficacy and safety analyses) includes all randomised subjects who received at least one dose of assigned medication. For efficacy analyses, subjects are being analysed by the randomised treatment group. At Week 40 analysis (the primary efficacy analysis time point), the primary hypothesis of the primary endpoint is to test whether there is a difference between the burosumab and active control groups in the mean RGI-C global scores at Week 40. An Analysis of Covariance (ANCOVA) model with treatment group adjusting for baseline rickets severity and age was used to test this hypothesis at a two-sided alpha level of 0.05. The proportion of RGI-C responders (subjects with mean RGI-C global score >=+-2.0) was summarised for each treatment group. At Week 64 (additional analysis), RGI-C global score over time will be analysed using the repeat measurement model that includes treatment group, visit, treatment group by visit interaction, and adjusted for baseline rickets severity and age. The change from baseline in RSS total score over time will be analysed at Week 40 and Week 64 using the same method as that of the RGI-C global score.
Primary outcomes (including scoring methods and timings of assessments)	Primary efficacy endpoint: Change from Baseline in severity of rickets as measured by RGI-C global score at Week 40.
Secondary outcomes (including scoring methods and timings of assessments)	The key secondary endpoints include: • Change in lower extremity skeletal abnormalities as assessed by the RGI-C long leg score • Change from baseline in standing height/recumbent length Z score • Change from baseline in RSS total score • Change in serum phosphorus from baseline to mean post-baseline values • Change from baseline in ALP For the growth-related endpoints RGI-C long leg score and change from baseline in standing height/recumbent length Z score, the primary assessment time will be Week 64. For other key secondary endpoints, the primary assessment time will be Week 40. Because of the small sample size, no multiplicity will be adjusted for the key secondary endpoints. Other Secondary Endpoints include: • Rickets Endpoint(s) o Proportion of subjects with a mean RGI-C global score ≥ +2.0 (substantial healing) o Change in rickets as assessed by RGI-C wrist and knee scores o Change from baseline in RSS wrist and knee scores • Growth Endpoint o Change in growth velocity Z score from pre-treatment to post-treatment • PD Endpoint(s) o Change from baseline over time in serum phosphorus o Number of subjects reach the normal range of serum phosphorus (3.2 - 6.1 mg/dL) over time o Change from baseline over time in serum 1,25(OH)2D, urinary phosphorus, TmP/GFR and TRP

	• Pain, Fatigue and Physical Function Endpoint(s) o Change from baseline in the PROMIS (Patient-Reported Outcomes Measurement Information System) scores in Pediatric Pain Interference, Physical Function Mobility and Fatigue domains o Change from baseline in the Faces Pain Scale – Revised (FPS-R) o Change from baseline in the Six Minute Walk Test (6MWT) total distance and percent of predicted normal

Abbreviations: XLH = X-linked hypophosphataemia; RSS = rickets severity score; PHEX = Phosphate-regulating neutral endopeptidase, X-linked; PTH = Parathyroid hormone; IWRS = Interactive Web Response System; PD = Pharmacodynamics; SD = Standard Deviation; SE = Standard Error; RGI-C = Radiographic Global Impression of Change; ALP = Alkaline phosphatase; PROMIS = Patient-Reported Outcomes Measurement Information System; FPS-R = Faces Pain Scale – Revised; 6MWT = Six Minute Walk Test; TmP/GFR = renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate; TRP = Transient Receptor Potential
Source: UX023-CL301 Statistical Analysis Plan; UX023-CL301 Protocol

Subject disposition

A total of 61 paediatric patients were enrolled into the study and were randomised 1:1 to burosumab (n=29) and conventional therapy (oral phosphate/active vitamin D; n=32). All patients completed the study to Week 40 and were included in the Full Analysis Set, Pharmacodynamic (PD) Analysis Set and Safety Analysis Set (Table 2).

Table 2. Patient disposition in Study 301

	Burosumab (n=29) n (%)	**Oral Phosphate/Active Vitamin D (n=32) n (%)**	**Overall (n=61) n (%)**
Subjects Randomised	[redacted]	[redacted]	[redacted]
Subject in Full Analysis Set	[redacted]	[redacted]	[redacted]
Subjects in Full Analysis Subset (Baseline Age ≥ 5 yrs)	[redacted]	[redacted]	[redacted]
Subject in PK Analysis Set	[redacted]	[redacted]	[redacted]
Subject in PD Analysis Set	[redacted]	[redacted]	[redacted]
Subjects in Safety Analysis Set	[redacted]	[redacted]	[redacted]
Subjects Completed Week 40	[redacted]	[redacted]	[redacted]
Subjects Discontinued Early Prior to Week 40	[redacted]	[redacted]	[redacted]

Abbreviations: PD = Pharmacodynamics; PK = Pharmacokinetics
Source: UX023-CL301 Biometrics tables (Week 40), Table 14.1.1

Demographic and baseline characteristics

Demographic and baseline characteristics were similar across the treatment groups (Table 3). Patients in the conventional therapy arm had received prior conventional therapy for [redacted] patients in the burosumab arm; they were [redacted] and had started conventional therapy [redacted]. Baseline height (z-score) was also lower in the burosumab arm.

Table 3. Demographics and Baseline Characteristics

	Burosumab Q2W (n = 29)	Conventional therapy (n = 32)	Overall (N = 61)
Age (years), mean (SD)	[redacted]	[redacted]	[redacted]
Sex, male n (%)	[redacted]	[redacted]	[redacted]
Race White Asian Other	[redacted]	[redacted]	[redacted]
Weight (kg), mean (SD)	[redacted]	[redacted]	[redacted]
Height (cm), mean (SD)	[redacted]	[redacted]	[redacted]
Standing Height (z-score), mean (SD)	[redacted]	[redacted]	[redacted]
Renal ultrasound score, (0 – 5 scale) – n (%) 0 1 2 3	[redacted]	[redacted]	[redacted]
Number (%) of Patients Who Received Prior Conventional Therapy	[redacted]	[redacted]	[redacted]
Duration of Prior Conventional Therapy (years), mean (SD)	[redacted]	[redacted]	[redacted]
Age When Conventional Therapy Was Initiated (years), mean (SD)	[redacted]	[redacted]	[redacted]
Pharmacodynamic parameters, mean (SD) Serum Phosphorus, mg/dL TmP/GFR (mg/dL) Serum 1,25(OH)2 D (pg/mL) ALP (U/L)	[redacted]	[redacted]	[redacted]
Rickets Severity RSS Total Score, mean (SD)	[redacted]	[redacted]	[redacted]

Abbreviations: SD = Standard Deviation; cm = centimetres; kg = kilograms; TmP/GFR = renal tubular maximum reabsorption rate of phosphate to glomerular filtration ratel ALP = Alkaline phosphatase; RSS = rickets severity score
Source: UX023-CL301 Biometrics tables (Week 40), Table 14.1.2.1.1.1

Efficacy

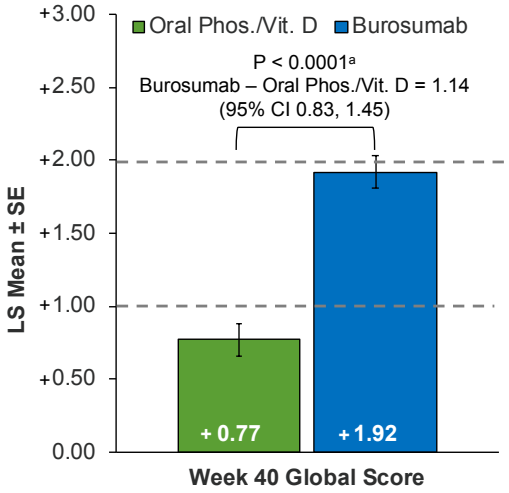
Effect of burosumab on rickets

RGI-C Scores

The study met its primary endpoint demonstrating that burosumab significantly improved rickets compared to conventional therapy, as assessed by three independent blinded paediatric radiologists using the RGI-C scale (Figure 3 and Table 4) (Ultragenyx Press Release, 2018).

The magnitude of effect was [redacted] (Table 5).

Figure 3. RGI-C Global Scores Week 40 (Full Analysis Set)



[a]ANCOVA model includes treatment and baseline age stratification as factors and baseline RSS as a covariate.
Source: Ultragenyx Press Release, 2018

Table 4. RGI-C Scores Week 40 (Full Analysis Set)

RGI-C Scores[a], LS mean (SE)	**Burosumab Q2W (n = 29)**	**Conventional therapy (n = 32)**	**Difference (95% CI)**	**p-value**
Global Score[b]	1.92 (0.110)	0.77 (0.107)	1.14 (0.83, 1.45)	p<0.0001
Knee Score[b]	[redacted]	[redacted]	[redacted]	[redacted]
Wrist Score[b]	[redacted]	[redacted]	[redacted]	[redacted]
Lower Limb Deformity Score[b]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LS = least squares; RGI-C = Radiographic Global Impression of Change
[a] The RGI-C score was based on a 7-point ordinal scale ranging from -3 (very much worse, or severe worsening of rickets) to +3 (very much better, or complete or near complete healing of rickets). The RGI-C were assessed by three independent blinded paediatric radiologists and the averaged values were used for analysis.
[b] LS Mean, SE, 95% CI and 2-sided p-value are from the analysis of covariance (ANCOVA) model that includes the RGI-C as the dependent variable, treatment group and baseline age stratification factor as independent variables, baseline RSS score as a continuous covariate
Source: Ultragenyx Press Release, 2018; UX023-CL301 Biometrics tables (Week 40), Table 14.2.1.1.1.1.

Table 5. RGI-C Scores Week 40 (subgroups by RSS total score and age)

Subgroup RGI-C Scores[a] LS mean (SE)	**Burosumab Q2W**	**Conventional therapy**	**Difference (95% CI)**
RSS Total score ≤2.5	[redacted]	[redacted]	[redacted]
Global Score[b]	[redacted]	[redacted]	[redacted]
RSS Total score >2.5	[redacted]	[redacted]	[redacted]
Global Score[b]	[redacted]	[redacted]	[redacted]
Age <5 years	[redacted]	[redacted]	[redacted]
Global Score[b]	[redacted]	[redacted]	[redacted]
Age ≥5 years	[redacted]	[redacted]	[redacted]
Global Score[b]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LS = least squares; RGI-C = Radiographic Global Impression of Change
[a] The RGI-C score was based on a 7-point ordinal scale ranging from -3 (very much worse, or severe worsening of rickets) to +3 (very much better, or complete or near complete healing of rickets). The RGI-C were assessed by three independent blinded paediatric radiologists and the averaged values were used for analysis.
[b] LS Mean, SE and 95% CI are from the analysis of covariance (ANCOVA) model that includes the RGI-C as the dependent variable, treatment group and baseline age stratification factor as independent variables, baseline RSS score as a continuous covariate
Source: UX023-CL301 Biometrics tables (Week 40), Table 14.2.1.1.2.1., 14.2.1.1.2.2., 14.2.1.1.3.1., 14.2.1.1.3.2.

Responder Analysis

Categorical analysis of RGI-C scores shows that whilst some patients treated with conventional therapy had worsening of their rickets, all patient in the burosumab arm experienced some healing of their rickets (i.e. had an RGI-C score of at least 1; Table 6). Substantial healing (RGI-C >= +2.0) was observed in 72% of patients receiving burosumab compared to 6% of patients receiving conventional therapy (Table 6 and Table 7). Similar results were observed across subgroups by age and RSS total score at baseline (Table 7).

Table 6. RGI-C Scores Week 40 (Categorical analysis)

RGI-C Scores at Week 40	**Burosumab Q2W**	**Conventional therapy**
-3, -2	[redacted]	[redacted]
-2,-1	[redacted]	[redacted]
-1,0	[redacted]	[redacted]
0,1	[redacted]	[redacted]
1,2	[redacted]	[redacted]
2,3	[redacted]	[redacted]

CI = confidence interval; LS = least squares; RGI-C = Radiographic Global Impression of Change
[a] The RGI-C score was based on a 7-point ordinal scale ranging from -3 (very much worse, or severe worsening of rickets) to +3 (very much better, or complete or near complete healing of rickets).
Source: Ultragenyx UX023-CL301 Biometrics tables (Week 40), Table 14.2.1.1.15.1.

Table 7. RGI-C Responder Analysis at Week 40 (Full Analysis Set, subgroups by RSS total score and age)

Responder[a] - %	Burosumab Q2W	Conventional therapy	OR (95% CI)	p-value
Full analysis set[b]	(n = 29) 72.4%	(n = 32) 6.3%	39.14 (7.24, 211.66)	p<0.0001
RSS Total score ≤2.5[b]	[redacted]	[redacted]	[redacted]	
RSS Total score >2.5[b]	[redacted]	[redacted]	[redacted]	
Age <5 years[b]	[redacted]	[redacted]	[redacted]	
Age ≥5 years[b]	[redacted]	[redacted]	[redacted]	

Abbreviations: RSS = rickets severity score; OR = Odds Ratio
[a] RGI-C responder is defined as patients with a mean RGI-C global score >= +2.0 (substantial healing of rickets).
[b] A logistic regression model includes treatment group and baseline age stratification factor as independent variables, baseline RSS total score as a continuous covariate. The estimated responder rate, 95% CI, odds ratio and 2-sided p-value are from the logistic regression model.
Source: UX023-CL301 Biometrics tables (Week 40), Table 4.2.1.1.8.1., 14.2.1.1.9.1, 14.2.1.1.9.2, 14.2.1.1.10.1., 14.2.1.1.10.2.

RSS Total Score Change from Baseline

Rickets severity was also assessed using the RSS scoring system, which showed that patients treated with burosumab showed a 2.8-fold improvement in rickets (RSS total score) compared to patients receiving conventional therapy. RSS total score was reduced by 64% in patients treated with burosumab vs. 23% with conventional therapy (Table 8).

Table 8. RSS Scores and Change from Baseline (Full Analysis Set)

RSS Score	Burosumab Q2W ((n = 29[b])	Conventional therapy (n = 32)	Difference (95% CI)[a]	p-value[a]
RSS Total Score				
Baseline, mean (SD)	3.16 (0.991)	3.19 (1.141)		
Week 40, mean (SD)	1.13 (0.715)	2.47 (1.092)		
Change to Week 40, LS mean (SE)[a]	-2.04 (0.145)	-0.71 (0.138)	-1.34 (-1.74, -0.94)	p<0.0001
RSS Knee Score				
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 40, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change to Week 40, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
RSS Wrist Score	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Week 40, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Change to Week 40, LS mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; LS = least squares; RSS = Rickets Severity Score; SD = Standard Deviation; SE = Standard Error; LS = Least Squares

[a] LS mean, SE, p value, and CI are from the ANCOVA model that includes treatment group and baseline age stratification factor as independent variables, baseline RSS score as a continuous covariate.

[b] One subject did not have RSS knee and total score rated at week 40 due to fused growth plates. The RSS total and knee numbers are based on n=28

Source: UX023-CL301 Biometrics tables (Week 40), Table 14.2.1.2.1.1

Table 9. RSS Total Score and Change from Baseline (Subgroups by RSS total score and age)

Subgroup RSS Total score	Burosumab Q2W[b]	Conventional therapy	Difference (95% CI)[a]
RSS Total score ≤2.5	[redacted]	[redacted]	
Baseline, mean (SD)	[redacted]	[redacted]	
Week 40, mean (SD)	[redacted]	[redacted]	
Change to Week 40, LS mean (SE)[a]	[redacted]	[redacted]	[redacted]
RSS Total score >2.5	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Week 40, mean (SD)	[redacted]	[redacted]	[redacted]
Change to Week 40, LS mean (SE)	[redacted]	[redacted]	[redacted]
Age <5 years	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Week 40, mean (SD)	[redacted]	[redacted]	[redacted]
Change to Week 40, LS mean (SE)	[redacted]	[redacted]	[redacted]
Age ≥5 years	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Week 40, mean (SD)	[redacted]	[redacted]	[redacted]
Change to Week 40, LS mean (SE)	[redacted]	[redacted]	[redacted]

CI = confidence interval; LS = least squares; RSS = Respiratory Severity Score; SD = Standard Deviation; SE = Standard Error
Source: UX023-CL301 Biometrics tables (Week 40), Table 14.2.1.2.2.1., 14.2.1.2.2.2., 14.2.1.2.3.1., 14.2.1.2.3.2.
[a] LS mean, SE, p value, and CI are from the ANCOVA model that includes treatment group and baseline age stratification factor as independent variables, baseline RSS score as a continuous covariate.
[b] One subject did not have RSS knee and total score rated at week 40 due to fused growth plates. The RSS total and knee numbers are based on n=28

Impact of burosumab on bone mineral metabolism

At baseline, patients in both the burosumab and conventional therapy arms had mean serum phosphorus levels and mean renal phosphate reabsorption levels below the lower limits of normal.

Serum phosphorus levels increased in patients treated with burosumab and were sustained throughout the study, with mean levels close to or in the low end of the normal range. In the oral phosphate/active vitamin D arm, mean serum phosphorus levels remained below the lower limits of normal over the 40-week period (Table 10 and Figure 4).

Renal phosphate reabsorption levels post-baseline through Week 40 were also in the normal range in the burosumab arm but remained below the lower limits of normal over the 40-week period in the oral phosphate/active vitamin D arm.

Table 10. Serum phosphorous levels and change from baseline

	Burosumab Q2W (n = 29)	Oral Phosphate/ Active Vitamin D (n = 32)	Difference (95% CI)[a]	p-value[a]
Serum Phosphorus (mg/dL)*				
Baseline, mean (SD)	2.42 (0.244)	2.30 (0.257)		
Post-baseline, mean (SD)[a]	3.38 (0.374)	2.55 (0.291)		
Change from baseline, LS mean (SE)	1.00 (0.062)	0.23 (0.058)	0.77	p<0.0001

*Serum phosphorus lower limit of normal: 3.2mg/dL
Source: Ultragenyx Press Release 2018
[a] The mean post-baseline is the average of serum phosphorous across weeks 1,4,8,16,24,32 and 40

Figure 4. Serum Phosphorus Level (mg/dL) (Mean ±SE) by Treatment Group (PD Analysis Set)

KRN23 = burosumab
Source: UX023-CL301 Biometrics figures (Week 40), Figure 14.2.3.1.1.

Patients in both the burosumab and conventional therapy arms demonstrated increases in serum 1,25-dihidroxy vitamin D, and maintained levels within the normal range through 40 weeks (Ultragenyx Press Release, 2018).

Mean TmP/GFR levels post-baseline through Week 40 were in the normal range in the burosumab arm but remained below the lower limits of normal over the 40-week period in the oral phosphate/active vitamin D arm (Figure 5). In the burosumab arm, [redacted] of patients had a TmP/GFR value within the reference range (2.6 to 4.4 mg/dL [0.84 to 1.42 mmol/L]) during the study, compared to [redacted] in the oral phosphate/active vitamin D arm.

Figure 5. TmP/GFR (mg/dL) (Mean ±SE) by Treatment Group (PD Analysis Set)

KRN23 = burosumab
Source: UX023-CL301 Biometrics figures (Week 40), Figure 14.2.3.3.1.

Serum Markers of Rickets – ALP

At Baseline, mean (SD) serum ALP levels were [redacted] U/L in the burosumab group and [redacted] U/L in the conventional therapy arm, well above the upper limit of the normal ranges for the ages of the children in this study (approximately 297 to 385 U/L, depending on the age and sex of the child). Treatment with burosumab showed a significant improvement in mean ALP levels into the normal range after 40 weeks of treatment with burosumab but ALP levels remained above the normal range in the conventional therapy arm ([redacted]; Figure 6).

Figure 6. ALP Level (U/L) (Mean ±SE) by Treatment Group (PD Analysis Set)

[a]Normal range varies depending on sex & age, within males and females ages 1-15, the upper limit ranged from 297 to 385 U/L
Source: UX023-CL301 Biometrics figures (Week 40), Figure 14.2.3.5.1.

Effect of burosumab on growth and walking ability

Patients treated with burosumab also demonstrated a greater numeric but not statistically significant improvement in growth and walking ability.

The difference in the change in growth velocity (Z score) between treatment groups was [redacted]

In the burosumab group, in patients aged 5 years or older, the distance walked in the six-minute walk test increased by [redacted] metres compared to [redacted] metres in the oral phosphate/active vitamin D arm, a difference of [redacted], GEE model; Figure 7).

Figure 7. Distance Walked in the Six Minute Walk Test (>5 years old)

aGEE model includes treatment, visit, treatment by visit interaction and baseline RSS stratification as factors and baseline 6MWT as a covariate, with exchangeable covariance structure.

[redacted]

Patient reported outcome data

PROMIS

The Patient-Reported Outcomes Measurement Information System (PROMIS) was developed by the National Institutes of Health and uses domain-specific measures to assess patient well-being. The domain-specific approach is based on the idea that health attributes, such as pain and physical function are not unique to a specific disease. The PROMIS contains a bank of questions from which relevant items can be extracted and used to create a custom form. The domains chosen to be relevant for the study were Pain Interference, Physical Function Mobility, and Fatigue domain scores.

PROMIS Pediatric Pain Interference, Physical Function Mobility and Fatigue domain scores (secondary efficacy endpoints in CL301), [redacted] (subjects ≥ 5 years of age at the Screening Visit; Figure 8 to Figure 10).

The minimal important difference (MID) may be calculated as half the value of the standard deviation at baseline (Norman, 2003). For the Pain Interference domain, the SD was [redacted]. At Week 40, the difference from baseline in the burosumab group was [redacted], and therefore reached the MID.

Figure 8. Change in PROMIS Pain Interference Domain Score from Baseline (Full Analysis Set, Baseline age ≥ 5 years)

KRN23 = burosumab
The LS Mean and SE are calculated from a generalized estimation equation (GEE) model including change from baseline in PROMIS domain score as the dependent variable, visit, treatment group, visit by treatment group and baseline RSS stratification as factors, baseline PROMIS domain score as a covariate, with exchangeable covariance structure.

Figure 9. Change in PROMIS Fatigue Domain Score from Baseline (Full Analysis Set, Baseline age ≥ 5 years)

KRN23 = burosumab
The LS Mean and SE are calculated from a generalized estimation equation (GEE) model including change from baseline in PROMIS domain score as the dependent variable, visit, treatment group, visit by treatment group and baseline RSS stratification as factors, baseline PROMIS domain score as a covariate, with exchangeable covariance structure.

Figure 10. Change in PROMIS Physical Function Mobility Domain Score from Baseline (Full Analysis Set, Baseline age ≥ 5 years)

KRN23 = burosumab
The LS Mean and SE are calculated from a generalized estimation equation (GEE) model including change from baseline in PROMIS domain score as the dependent variable, visit, treatment group, visit by treatment group and baseline RSS stratification as factors, baseline PROMIS domain score as a covariate, with exchangeable covariance structure.

Faces Pain Scale

The Faces Pain Scale – Revised (FPS-R) is a self-reported measure of pain intensity developed for children and has been validated for use in children 5 to 16 years of age. The FPS-R graphically depicts pain intensity using faces with scores chosen from 0, 2, 4, 6, 8, and 10 (0=no hurt; 10=hurts worst). Pain intensity measured by the change from baseline in the FPS-R (for subjects ≥ 5 years of age at the Screening Visit) was a secondary endpoint in CL301.

SF-10

Change from baseline in the SF-10 for Children Health Survey (SF-10; for subjects ≥ 5 years of age at the Screening Visit) was an exploratory endpoint in CL301. (Figure 11). The MID, calculated as half of the SD at baseline, is , and therefore the MID was reached in the burosumab arm.

(Figure 12).

Figure 11. Change in SF-10 Physical Summary Score from Baseline

KRN23 = burosumab

Figure 12. Change in SF-10 Psychosocial Summary Score from Baseline

KRN23 = burosumab

Safety

The burosumab safety profile observed in this study was generally consistent with that seen in other burosumab paediatric XLH studies. There were no treatment discontinuations and no deaths reported in the study (Table 11).

[redacted]

Table 11. Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)

	Burosumab (n = 29) n (%)	**Oral Phosphate/Active Vitamin D (n = 32) n (%)**
Treatment-Emergency Adverse Event (TEAE)	[redacted]	[redacted]
Serious TEAE	[redacted]	[redacted]
Related TEAE	[redacted]	[redacted]
Serious Related TEAE	[redacted]	[redacted]
Grade 3 or 4 TEAE	[redacted]	[redacted]
TEAE Leading to Study Discontinuation	[redacted]	[redacted]
TEAE Leading to Treatment Discontinuation	[redacted]	[redacted]
TEAE Leading to Death	[redacted]	[redacted]

Source: UX023-CL301 Biometrics tables (Week 40), Table 14.3.1.1.1.

The most frequent treatment-emergent adverse events (TEAEs) in the burosumab group (by preferred term, >30% incidence) were [redacted] (Table 12).

In the burosumab arm, 45% of patients had injection site reactions (grouped terms), all but one were mild and none were considered serious (Ultragenyx Press Release, 2018).

Table 12. Summary of Treatment Emergent Adverse Events (Frequency ≥10% in the Burosumab Arm) by System Organ Class and Preferred Term (Safety Analysis Set)

Preferred Term	Burosumab (n = 29) n (%)	Oral Phosphate/Active Vitamin D (n = 32) n (%)
Subjects with any TEAE	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Hypersensitivity[a]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Injection site reaction[b]	[redacted]	[redacted]
Tooth abscess	[redacted]	[redacted]
Vitamin D decreased[c]	[redacted]	[redacted]
Dental caries	[redacted]	[redacted]
Rhinorrhoea	[redacted]	[redacted]
Asthma	[redacted]	[redacted]
Contusion	[redacted]	[redacted]
Influenza	[redacted]	[redacted]
Oropharyngeal pain	[redacted]	[redacted]
Seasonal allergy	[redacted]	[redacted]
Toothache	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
Ear pain	[redacted]	[redacted]
Nasal congestion	[redacted]	[redacted]
Rash[d]	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]
Teething	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]

Source: UX023-CL301 Biometrics tables (Week 40), Table 14.3.1.2.1

[a] Includes Preferred Terms (PTs) of: Injection site rash, Rash, Injection site urticaria, Dermatitis allergic, Drug eruption, Hypersensitivity, Injection site hypersensitivity, Rash erythematous, Rash generalised, and Swelling of face. Note: Injection site rash, Injection site urticaria, and Injection site hypersensitivity are also included in the search for Injection Site Reaction TEAEs

[b] Includes PTs of: Injection site reaction, Injection site erythema, Injection site pruritus, Injection site rash, Injection site erosion, Injection site swelling, Injection site urticaria, Injection site discomfort, Injection site hypersensitivity, Injection site inflammation, and Injection site papule.

[c] Includes PTs of: Vitamin D decreased, Vitamin D deficiency, and Blood 25-hydroxycholecalciferol decreased

[d] Includes PTs of: Rash, Rash erythematous and Rash generalised. Note: these PTs are also included in the search for Hypersensitivity TEAEs

Adverse Events by Relationship to Investigational Product

TEAEs related to treatment (i.e., TEAEs deemed “definitely,” “probably,” or “possibly” related to study drug by the investigator) are shown in Table 13. Events reported at a greater frequency (≥10% difference) in the burosumab arm compared to the oral phosphate/active vitamin D arm were [redacted]

Table 13. Summary of Treatment Related Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Burosumab (n=29) n (%)	Oral Phosphate/ Active Vitamin D (n=32) n (%)
Subjects with any treatment-emergent adverse event	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]
Injection site pruritus	[redacted]	[redacted]
Injection site rash	[redacted]	[redacted]
Injection site swelling	[redacted]	[redacted]
Injection site urticaria	[redacted]	[redacted]
Injection site discomfort	[redacted]	[redacted]
Injection site erosion	[redacted]	[redacted]
Injection site hypersensitivity	[redacted]	[redacted]
Injection site inflammation	[redacted]	[redacted]
Injection site papule	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Scoliosis	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Tooth abscess	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Dental caries	[redacted]	[redacted]
Mouth ulceration	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Toothache	[redacted]	[redacted]
Change of bowel habit	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Frequent bowel movements	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Erythema	[redacted]	[redacted]
Rash generalised	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Injection related reaction	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Flushing	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]
Blood phosphorus decreased	[redacted]	[redacted]

Source: UX023-CL301 Biometrics tables (Week 40), Table 14.3.1.4.1

No clinically meaningful changes were observed in mean serum calcium and serum intact parathyroid hormone in either treatment arm. No clinically significant changes were observed in renal ultrasounds pre-and post-treatment in either treatment arm (Ultragenyx Press Release, 2018).

[redacted]

References

Norman, G et al. Interpretation of Changes in Health-Related Quality of Life: The Remarkable Universality of Half a Standard Deviation. Medical Care 2003; 41 (5): 582-592

Ultragenyx. Press Release: Ultragenyx and Kyowa Kirin Announce Topline Phase 3 Study Results Demonstrating Superiority of Crysvita® (burosumab) Treatment to Oral Phosphate and Active Vitamin D in Children with X-Linked Hypophosphatemia (XLH). May 2018. Available at: http://ir.ultragenyx.com/news-releases/news-release-details/ultragenyx-and-kyowa-kirin-announce-topline-phase-3-study. Accessed June 2018.

Ultragenyx. UX023-CL301 Biometrics tables (Week 40). April 2018.

Ultragenyx. UX023-CL301 Biometrics figures (Week 40). April 2018.

Ultragenyx. Study Protocol: A Randomized, Open-Label, Phase 3 Study to Assess the Efficacy and Safety of KRN23 Versus Oral Phosphate and Active Vitamin D Treatment in Pediatric Patients with X-linked Hypophosphatemia (UX023-CL301). April 2016.

Appendix B: Economic Analysis

The company's original base case resulted in an ICER of [redacted] with [redacted] undiscounted incremental QALYs. Further to the originally submitted analysis, the updated economic analysis for burosumab includes the following amendments:

- Use of ERGs preferred method of calculation of transition probabilities
- Inclusion of costs of adverse events associated with burosumab, as preferred by the ERG
- Inclusion of Phase 3 data within transition probabilities
- Amendment to age at which treatment is stopped, to reflect the ECD and discussion at committee meeting
- Amendment to the calculation of utilities during childhood
- Incorporation of new long-term utilities in adulthood

Note that a discount rate of 1.5% is used as per the original company model, in line with the new data supporting the long-term outcomes in adulthood and maintaining patients to near full health. Following these amendments, the list price ICER is [redacted] with [redacted] undiscounted incremental QALYs (Table 13). With a patient access scheme, the ICER is reduced to [redacted].

In addition, scenario analysis explores the following scenarios:

1. Use of a 3.5% discount rate (PAS ICER [redacted])
2. Assuming treatment stops at the ages of 16 in girls and 17 in boys (PAS ICER [redacted])
3. Including caregiver disutilities (PAS ICER [redacted])
4. Most conservative scenario: use of a 3.5% discount rate, assuming treatment stops at the ages of 16 in girls and 17 in boys, no inclusion of long-term utility changes (PAS ICER [redacted])

This document outlines the revisions made.

Incorporation of data from Phase 3 study

The ERG corrected the methodology for estimating transition probabilities matrices in the original submission. We have subsequently applied the ERG's preferred approach to the revised model.

Furthermore, we apply this method to the additional clinical evidence of burosumab comprising week 40 results of Study CL301. Full details of the study are provided in the accompanying appendix to the ECD response. The transition probabilities were calculated from the total RSS scores (wrist and knee) of patient level observations at baseline and week 40. One patient was excluded from the analysis in the burosumab arm due to absence of week 40 data. Using the same method and software as the ERG, the 40 week transitions for burosumab (Table 1) have been converted to one-year transition probabilities (Table 2).

As the inclusion criteria for Study CL301 were XLH patients with a demonstrated radiographic evidence of rickets of ≥ 2.0 points RSS total score, there are no observations of patients in the healed or mild health state at baseline. Thus utilising only the CL301 data for transition probabilities would not provide the full set of transitions needed for the model. To model transitions between all the health states of the economic model, data from CL301 has been combined with the results from CL201 and CL205. The expected 1-year observation matrix has been calculated by redistributing the patients in each study across each of the annualised probability matrices from CL301, CL201 and CL205 calculated in R. The expected 1-year observation matrix for CL301 is provided in Table 3. The three expected 1-year observations were combined together (Table 4). The final probability matrix used for burosumab is given in Table 5.

Table 1. Observation matrix for burosumab (Study CL301, baseline to week 40)

Week 40 / Baseline	Mild	Moderate	Severe	Healed	Total
Mild	0	0	0	0	0
Moderate	2	1	0	0	3
Severe	16	8	1	0	25
Healed	0	0	0	0	0

Table 2. Transition probability matrix for burosumab, using Study CL301 data

	Mild	Moderate	Severe	Healed
Mild				
Moderate	76%	24%	0%	0%
Severe	74%	24%	2%	0%
Healed				

Table 3. Expected 1-year observation matrix for burosumab (Study CL301), calculated by multiplying Table 1 and

Table 2

	Mild	Moderate	Severe	Healed	Total
Mild					
Moderate	2.3	0.7	0.0	0.0	3
Severe	18.5	6.0	0.5	0.0	25
Healed					

Table 4. Expected 1-year observation matrix for burosumab, combined data from Study CL201, CL205 and CL301

	Mild	Moderate	Severe	Healed	Total
Mild	5.6	0.0	0.0	3.4	9
Moderate	7.4	5.9	0.0	0.7	14
Severe	29.4	12.8	0.5	0.3	43
Healed	0.0	0.0	0.0	1.0	1

Table 5. Transition probability matrix for burosumab, combined data from Study CL201, CL205 and CL301

	Mild	Moderate	Severe	Healed
Mild	100%	0%	0%	0%
Moderate	76%	24%	0%	0%
Severe	71%	27%	3%	0%
Healed	0%	0%	0%	100%

The corresponding 40 week observed transitions and annualised probabilities are given in Table 6 and Table 7, respectively. As with the burosumab data, utilising only the CL301 control arm data for transition probabilities for standard of care (SoC) would not provide the full set of transitions needed for the model. To model transitions between all the health states of the economic model, the control arm data from CL301 has been combined with the previous data used to generate transition probabilities for SoC: the UK chart review data, assuming last observation carried forward (LOCF). The expected 1-year transition matrix is given in Table 8. The final probability matrix used for SoC is given in Table 9.

Table 6. Observation matrix for SoC (Study CL301, baseline to week 40)

Week 40 / Baseline	Mild	Moderate	Severe	Healed	Total
Mild	0	0	0	0	0
Moderate	1	5	1	0	7
Severe	3	7	15	0	25
Healed	0	0	0	0	0

Table 7. Transition probability matrix for SoC, using Study CL301 data

	Mild	Moderate	Severe	Healed
Mild				
Moderate	18%	64%	18%	0%
Severe	15%	35%	50%	0%
Healed				

Table 8. Expected 1-year observation matrix for SoC, using combined data from UK chart review – LOCF with CL301

	Mild	Moderate	Severe	Healed	Total
Mild	31.0	5.0	4.0	4.0	44
Moderate	10.3	39.5	6.3	2.0	58
Severe	8.8	19.7	87.5	4.0	120
Healed	1.0	1.0	2.0	10.0	14

Table 9. Transition probability matrix for SoC, using combined data from UK chart review (LOCF) with CL301

	Mild	Moderate	Severe	Healed
Mild	70%	11%	9%	9%
Moderate	18%	68%	11%	3%
Severe	7%	16%	73%	3%
Healed	7%	7%	14%	71%

Age at which treatment ceases

The committee discussed the uncertainty around the age at which patients might stop burosumab treatment. Kyowa Kirin accepts that the timing of this would vary between people. Bone maturity relative to chronical age is considered an important aspect to evaluate when epiphyses have closed, and growth is complete. However, growth velocity may be a better interim growth measure than skeletal maturity at a particular age as bone maturity may come at the expense of early closure of the epiphyses. The

clinical experts at the committee meeting indicated that measures of final height can be defined as a growth velocity that has slowed to less than a defined amount of <2cm per annum, in line with current guidelines around growth hormones.

The model had previously assumed that growth stops before the age of 17 in girls and before the age of 18 in boys. In fact, the RCPCH growth charts indicate that growth slows to <2cm per annum before the age of 15 in girls (Figure 1) and before the age of 17 in boys (Figure 2). Therefore, in the revised analysis treatment with burosumab is assumed to occur up to, and including, the age of 14 years of in girls, and 16 years in boys. This is aligned to data submitted as part of the NICE TA188 for growth hormone, which indicated that treatment ceased at between 14 and 16 years (Takeda et al. 2009). Scenario analysis is conducted to explore how the age of stopping treatment impacts results.

Figure 1. UK growth charts will growth velocity, girls

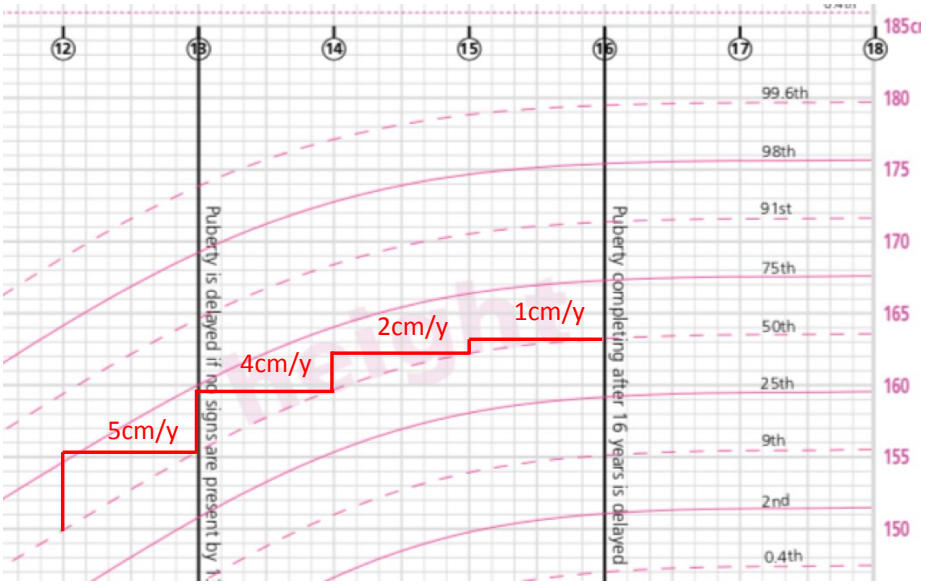
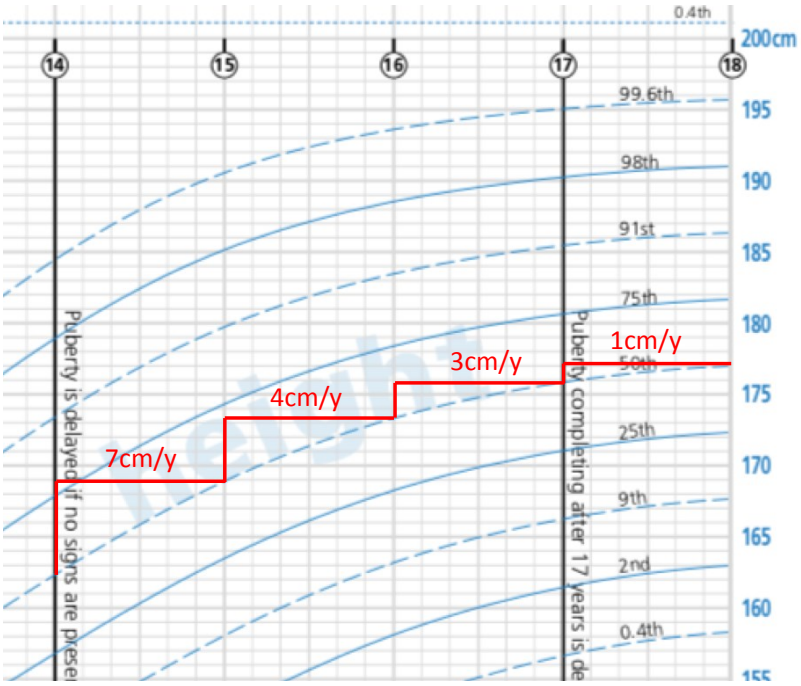


Figure 2. UK growth charts will growth velocity, boys



Utilities during childhood

ECD Section 4.20: To model health-related quality of life, the company conducted a utility study in which vignettes describing the modelled health states were developed. The ERG highlighted that the company made adjustments to the utility values in the published report of the study because not all experts provided estimates for all health states. It was not convinced that it was necessary to adjust the utility values, but had very little evidence on which to choose whether to use the adjusted or unadjusted utility values. On balance, the committee concluded that it would be more appropriate to consider analyses based on the unadjusted utility values in its decision making.

Of the seven clinical experts that participated in the vignette study, two experts did not provide estimates for the healed health state and a different two experts did not provide estimates for the severe health state. The reason for adjustment is that the clinical experts each have a different perception of what 'baseline' may be and when there are missing values, the results can be skewed by these underlying differences in the baseline. The individual health state valuations of the respondents are illustrated in Figure 3. It is clear that respondent 1 believes XLH patients have a relatively high quality of life and thus their perception increases average values for the mild, moderate and severe states, but not the healed state because they did not provide an estimate. Given it is the incremental difference between the health states that is of interest, rather than the baseline, we adjusted the utilities to reflect this.

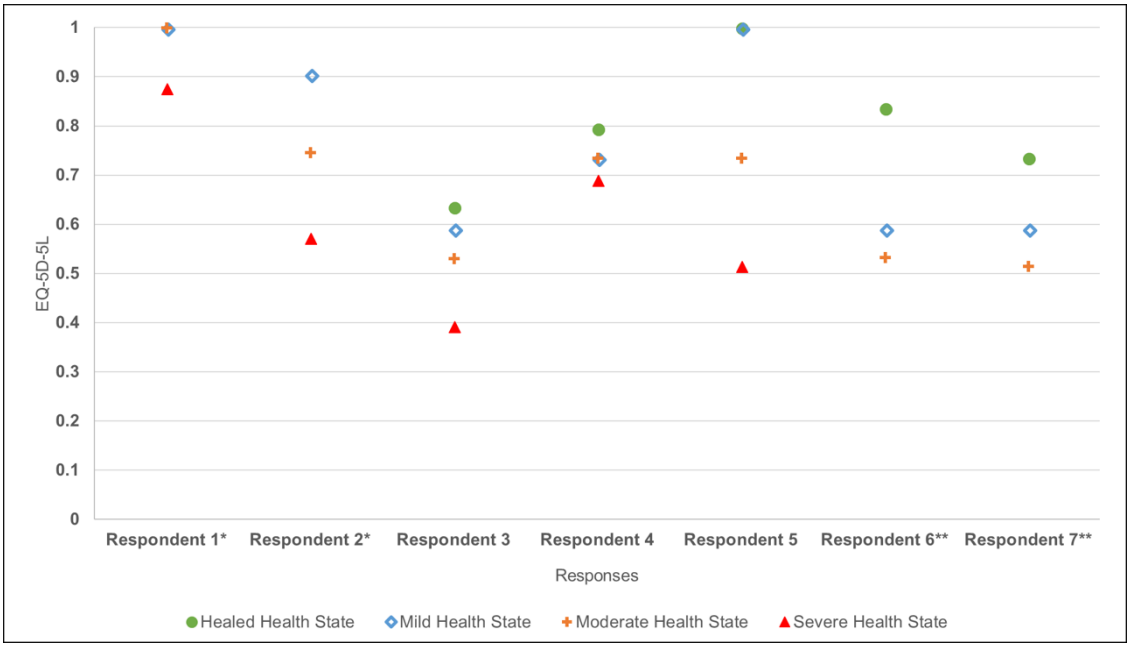
However, we appreciate that there is limited evidence on which to judge whether such adjustments should be made. Therefore, we have not adjusted the calculations (as

preferred by the committee) and have instead re-contacted the clinical experts that had missing values in an attempt to gain a full dataset. The two clinical experts that had not given values for the severe states had done so because they hadn't seen patients in those two states and struggled to visualise such a patient. Therefore, these missing values could not be obtained. One of the clinical experts was not able to provide a value for the healed health state within the duration of the consultation.

The remaining clinical expert that hadn't provided a healed health state value is participating in the NICE process and so declined further participation in the study over concerns of being conflicted. However, upon inspection of the utilities obtained during the original study, it was found that this expert had actually scored the mild and moderate states with the highest possible value (1.0). Since utilities cannot be greater than 1 and patients in the healed state wouldn't have a worse quality of life than those in the mild or moderate states, then it can be inferred that this clinical expert would have scored the healed state with 1.

The impact of imputing this missing value on the overall utility values is shown in Table 10.

Figure 3. Variation in response from vignette study (Lloyd et al. 2018)



*Missing data for healed health state; **Missing data for severe health state

Table 10: Utilities by health state and age group

		Company submission (adjusted)	ERG (unadjusted)	Revised company submission (unadjusted)
Age 1-4	Healed rickets	0.872	0.800	0.834
Age 1-4	Mild	0.774	No change	No change
Age 1-4	Moderate	0.685	No change	No change
Age 1-4	Severe	0.546	0.610	0.610
Age 5-12	Healed rickets	0.969	0.890	0.909
Age 5-12	Mild	0.757	No change	No change
Age 5-12	Moderate	0.613	No change	No change
Age 5-12	Severe	0.521	0.602	0.602
Age 13+	Healed rickets	0.861	0.811	0.843
Age 13+	Mild	0.671	No change	No change
Age 13+	Moderate	0.575	No change	No change
Age 13+	Severe	0.462	0.479	0.479

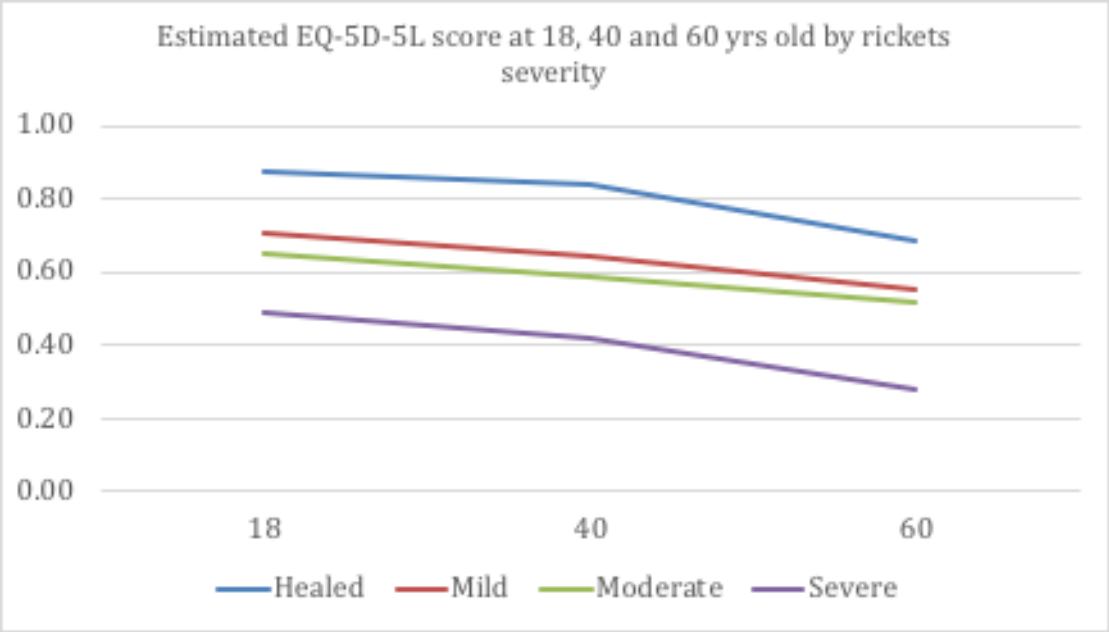
Long-term outcomes: Utilities during adulthood

The committee has acknowledged that there is lifetime benefit for people treated with burosumab because it can prevent irreversible bone damage, but have concerns that the long-term consequences of the progressive bone disease and ongoing metabolic symptoms of XLH, which would not be affected by burosumab, are uncertain. The committee considered that the ERG's approach to apply an arbitrary decrement at 20 years was purely illustrative of the potential effect of the assumption of disease stabilisation. To provide more estimates of long-term utilities rather than arbitrarily assuming a decline, a further study was conducted.

An extension of the vignette study was conducted with clinical experts of adult patients (rather than paediatric, as previously) to elicit health utilities to explore the prognosis of adults with different levels of severity of XLH at different stages of adulthood. Full details of the study are available in a report (Lloyd et al. 2018). Validation and valuation of the health states of interest (severe, moderate, mild and healed rickets) was completed through a series of interviews with five UK clinical experts.

Each participant reviewed every case study. Each case study presented involved asking the participant to imagine an adult in the specified age group (18 years old, 40 years old and 60 years old) with a level or severity of XLH (severe, moderate, mild and healed rickets) and consider the impact of the disease on different aspects of HRQL using the EQ-5D-5L. The utilities derived from the study show a predicted decline in HRQL from 18 to 60 years of age with increasing severity of rickets (Figure 4).

Figure 4. Results of the vignette extension study exploring utilities in adulthood (Lloyd et al. 2018)



The magnitude of the decline is greater than the decline seen in the quality of life of the general population. These deteriorations over time were attributed to co-morbidities associated with XLH disease progression, with the development of osteoarthritis, osteomalacia and other functional complications. The decline was greatest in the severe health states, supporting the hypothesis that an aligned skeleton at the end of growth will result in fewer further complications during adulthood.

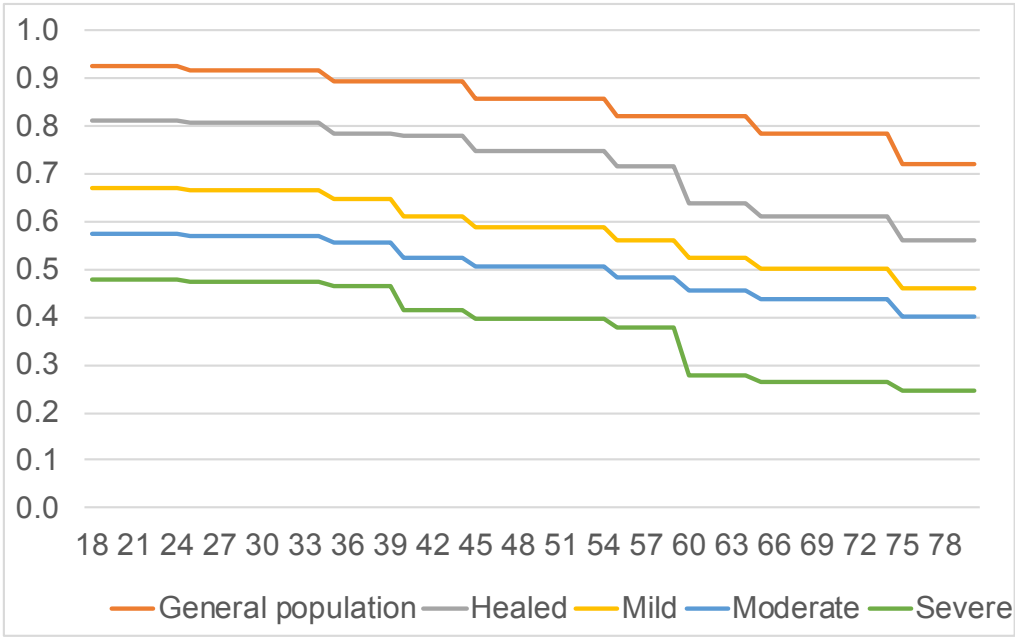
With the small number of clinical experts interviewed that valued the health states, variation is observed around the mean values. The clinical experts cared for XLH patients between 6 and 30 years, and it was observed that it was qualitatively challenging to predict the impact of the disease on patients based on the state of their disease at the age of 18. Nevertheless, there was a general consensus that preventing spinal stenosis prior to adulthood would enable a more positive prognosis in life.

At the age of 40, patients that had healed rickets at the end of growth were estimated to have a utility of 0.84, compared to 0.89 in the general population. At the age of 60, patients that had healed rickets at the end of growth were estimated to have a utility of 0.69, compared to 0.82 in the general population. The quality of life predicted by the clinical expert vignette study at the age of 40 and 60 was used to update the model to more accurately predict long-term quality of life impacts of disease progression. The declines at the age of 40 and 60 were applied in addition the general population decline in quality of life (Table 11; Figure 5).

Table 11. Age-dependent utility multipliers associated with XLH derived from the vignette study by health state severity

Age (years)	Healed	Mild	Moderate	Severe
12 - 24	1.000	1.000	1.000	1.000
25-34	0.992	0.992	0.992	0.992
35-39	0.966	0.966	0.966	0.966
40-44	0.959	0.909	0.913	0.863
45-54	0.922	0.875	0.878	0.830
55-59	0.881	0.836	0.839	0.793
60-74	0.752	0.748	0.759	0.554
75+	0.689	0.686	0.696	0.508

Figure 5. Utilities by age applied in the revised economic analysis, using declines from vignette-derived utilities at the age of 40 and 60, in addition to general population quality of life declines



It should be noted that the clinical experts observed that it was qualitatively challenging to predict the long-term impact of the disease based only on patients' status at the age of 18. This could be a reason for the study producing inconsistent quality of life valuations compared to additional new data from a UK natural history study of adults with XLH.

Additional data comes from an analysis of data collected as part of the RUDY database (a study of rare diseases by the University of Oxford. Mean EQ-5D values from a 2016 publication of this study (Forestier-Zhang et al. 2016) were included in the submission.

[redacted]

[redacted] This might suggest that the cost-effectiveness model overpredicts the disease progression in both arms of the model. However, the RUDY database is not limited to patients that were showing radiological evidence of rickets during growth and therefore could be milder than the population under consideration for burosumab.

Table 12. EQ-5D-5L baseline utility scores stratified by age from XLH patients in RUDY

Age group	Age range	Observations	Mean	Std. Dev.	Min	Max
10	10-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	20-29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	30-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	50-59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	60-69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70	70-79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80	80-89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Scenario analysis: Applying a discount rate of 3.5%

The committee concluded after the first committee meeting that the criteria for deviating from a 3.5% discount rate were not met due to likelihood of the disease progression and symptoms in adulthood. The evidence on long-term benefit presented in this ECD response clearly demonstrates that disease progression in adulthood will not be significant and patients that have a healed skeleton at the end of growth will have quality of life that is much closer to the general population than patients receiving current therapy (see Figure 5).

A discount rate of 1.5% should be used on the basis that burosumab meets the following criteria:

- Treatment enables patients to have a near full-health, where they otherwise would have had a very severely impaired life
- This is effect is sustained across their lifetime (more than 30 years)
- It is highly likely that the long-term health benefits are likely to be achieved given the robust evidence on long-term outcomes presented in this submission
- The treatment does not commit the NHS to significant irrecoverable costs

During the recent HST appraisal of Strimvelis (HST7), the committee considered that it was likely that the alternative 1.5% discounting rate was intended to cover situations when costs are incurred up-front, but benefits are accrued over a longer period. This is comparable to burosumab, in which the costs are incurred in childhood resulting in lifelong benefits. Furthermore, the 2018 release of the HM Treasury Green Book specifically states that QALYs should be discounted at a rate of 1.5%.

We maintain that the assessment of burosumab reflects the case for which the use of an alternative discount rate was established i.e. significant long-term benefits accruing over a patient's lifetime. Therefore, the revised economic analysis continues to apply a 1.5% discount rate. However, we explore scenario analyses applying a discount rate of 3.5% to both costs and outcomes.

Scenario analysis: Including carer disutilities

In the committee meeting, it was recognised that caring for a family member with XLH confers a burden on the caregiver, and their quality of life. Both adults with XLH and parents of patients expressed that the reliance on others that XLH causes seriously affects the everyday lives of carers. As well as impacting on their day to day activities it has a psychological effect, with parents feeling responsible for the suffering of their children.

It was discussed that with disease progression, XLH can result in patients being potentially bedbound or wheelchair dependent. Parents of children with activity limitations, disabilities and chronic conditions experience increased emotional stress

and the added burden of care and other parenting responsibilities associated with a child's health and functional status create additional stress for parents (Smith et al. 2002; Dyson 1997; Patterson et al. 1992). It has been observed that informal caregivers of patients with Pompe disease that are wheelchair dependent experience a higher degree of caregiver burden (Kanters et al. 2013).

To explore the impact of including caregiver disutilities in the model, a review of the literature was conducted to identify potential values from comparable conditions. Wittenberg et al conducted a systematic review of disutilities of illness for caregivers and families in 2013. Of the studies explored in this review, a caregiver disutility -0.08 (SE 0.01) described by Kuhlthau and colleagues was identified as a reasonable estimate of the disutility of a caregiver of an XLH patient as it was based on one caregiver of a patient with limited activity (Kuhlthau et al. 2010). It has been assumed that this disutility of 0.08 would apply to patients in the moderate and severe health states up to the age of 18.

Revised base-case results and scenario analysis

The results of the revised economic analysis are presented at list price (Table 13) and the new PAS price (Table 14). The incremental impact of each change between the original and revised model is explored, along with scenario analyses. The results show that, with the patient access scheme, burosumab remains cost-effective.

Table 13: Step-by-step modifications from original base case to revised base-case, with results (without PAS)

Scenario / change	Total costs (£)		Total QALYs		Incremental costs (£)	Incremental QALYs	ICER (£)	Undiscounted QALYs
	Burosumab	SoC	Burosumab	SoC				
Company original base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use of ERGs preferred method of calculation of transition probabilities and inclusion of adverse event costs for burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Include CL301 study data into transition probabilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Set the age at treatment termination in line with the stopping rule of growth velocity <2cm per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised utilities during childhood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply progressive utilities during adulthood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final revised model at 1.5% discount rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Further scenario: Including caregiver disutilites	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Further scenario: 3.5% discount rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conservative scenario - original model but with:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

• use of ERGs preferred method of calculation of transition probabilities and inclusion of adverse event costs for burosumab • Include CL301 study data into transition probabilities • Revised utilities during childhood • a 3.5% discount rate								

**This is the model that was presented in response to the ERG clarification questions, which included the correction of minor errors*

Table 14: Step-by-step modifications from original base case to revised base-case, with results (with PAS)

Scenario / change	Total costs (£)		Total QALYs		Incremental costs (£)	Incremental QALYs	ICER (£)	Undiscounted QALYs
	Burosumab	SoC	Burosumab	SoC				
Company original base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use of ERGs preferred method of calculation of transition probabilities and inclusion of adverse event costs for burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Include CL301 study data into transition probabilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Set the age at treatment termination in line with the stopping rule of growth velocity <2cm per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised utilities during childhood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply progressive utilities during adulthood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final revised model at 1.5% discount rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Further scenario: Including caregiver disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Further scenario: 3.5% discount rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conservative scenario as detailed in Table 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Comments on Burosumab for X-linked Hypophosphataemia - on behalf of British Paediatric & Adolescent Group and Birmingham Women's & Children's NHS Foundation Trust

1. We think the clinical evidence that is currently available and our own experiences indicates that the drug is very effective and safe with minimal side effects. We recognise that there is at present limited long term data but the provisional results of the Phase 3 Clinical Trial which compares the drug to conventional treatment are extremely positive in favour of Burosumab. We would recommend that the Committee do not make a decision until they have had the opportunity to review the data from the Phase 3 clinical trial.
2. We do not feel that the improvement in the quality of life for children with XLH receiving this drug has been considered. Those patients and their families who are now receiving Burosumab have commented that their life is much improved now they do not have to take medication five times a day.
3. We recognise that the cost of the drug is extremely expensive and significantly more than conventional treatment. We would hope that negotiation with the drug company could lead to a significant reduction in the cost so that it is available for all children with XLH who would benefit from treatment.
4. We recognise that there is a risk of wastage of a very expensive drug with the current ampoules that are available. We would therefore like to see the development of a multidose delivery device to reduce the risk of wastage.
5. The evaluation has not taken account of the potential reduction in costs related to the current management of XLH. This would include a reduction in the need for orthopaedic surgery to correct bowing deformities of the legs and the potential reduction in the development of dental abscesses. In addition it is likely there will an improvement in growth with this drug so that short stature as a child or adult with XLH will be reduced. There are less likely to be side effects seen with conventional therapy such as nephrocalcinosis and hyperparathyroidism.

METABOLIC SUPPORT UK
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www.metabolicsupportuk.org

6th July 2018

Dear Evaluation Committee

Metabolic Support UK response to draft guidance on burosumab for treating X-linked hypophosphataemia (ID1151)

Metabolic Support UK, as the umbrella patient organisation for Inherited Metabolic Disorders, is disappointed that NICE does not recommend re-imbursement of the treatment burosumab for X-linked Hypophosphatemia (XLH) in children and young people following the recent Highly Specialised Technologies evaluation.

Burosumab is the first and only treatment to target the underlying pathophysiology of XLH. An injection given every two weeks from the age of one until the skeleton stops growing, aims to increase reabsorption of phosphate from the kidney and, through vitamin D production, improve intestinal absorption of calcium and phosphate.

Metabolic Support UK has seen the positive impact on XLH patients who have received the treatment under the clinical trials and early access scheme. Parents of children that have benefitted from the treatment report strong improvements in adherence to the treatment pathway, physical functioning, mobility, bone density and straightening, pain levels and social inclusion; overall impacting on the quality of life and mental wellbeing not just for the patient but their parents/carers and wider family.

Clinical experts stated, during the Committee meeting, the clear benefits of the treatment for all children affected by XLH and that early treatment would reduce the need for surgical intervention and avoidable suffering.

While we are pleased that the Committee recognises the meaningful clinical benefits of burosumab and the lasting effect over the patient's lifetime, due to the prevention of irreversible bone damage, we do not feel that the long-term benefits when patients reach adulthood have been fully considered. Though the marketing authorisation for burosumab does not include adults, early access to, and adherence of, this treatment during the pivotal bone growth years could bring substantial benefits post-adolescence.

We believe the Committee's conclusion stated in 4.13 'burosumab would not improve other aspects of XLH in the long-term' does not address the fact that fixing or correcting skeletal deformities during childhood will see the improvements continue into adulthood. Adult patients successfully treated as children will see an improvement in the lifelong disability, a reduced need

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for corrective surgery and experience less debilitating pain and mobility issues. The social and psychological benefits seen by patients on the clinical trial as a result of the physical improvements will also continue into adulthood, reducing the burden of care in the long-term.

Metabolic Support UK has engaged and endeavoured to bring the patient voice and experience into the process where possible. The data and evidence in this area is limited, in common with all products considered under the current Highly Specialised Technology appraisal process. We hope that NICE, NHS England and all stakeholders can work together to agree a way to ensure patients will receive access to this important treatment that would have a substantial impact on quality of life and ability to participate in everyday activities over a lifetime.

Yours sincerely

Joanne Taylor
Acting Chief Executive, Metabolic Support UK

Oliver Gardiner
XLH UK
[redacted]

06/07/2018

Burosumab for treating X-linked hypophosphataemia [ID1151]

Dear Evaluation Committee,

XLH UK, a charitable trust registered in England and Wales, and The XLH Network Inc., a non-profit patient advocacy group incorporated in the United States and representing patients and their families worldwide, as patient organisations for those suffering with X-Linked Hypophosphataemia, are disappointed that NICE does not currently recommend burosumab for children and young people with X-Linked Hypophosphataemia (XLH) following the recent Highly Specialised Technologies draft evaluation ID1151.

Burosumab offers a life-changing moment for XLH patients as it is the first and only treatment that targets the underlying mechanism of their hypophosphataemia. The trial results demonstrate strong improvements in the areas that matter most to patients, including reductions in daily pain and stiffness as well as improvements in healing of fractures and rickets severity which may limit the eventual need for repeated, invasive, corrective surgeries.

We sincerely urge NICE to reconsider their decision and make this new and truly life-changing treatment available to paediatric patients (and eventually to adults), as it can not only heal rickets in all patients, but it drastically reduces chronic pain, dental abscess risk, fatigue, and the need for surgical intervention.

While we understand that medical decisions require scientific evidence, it is already absolutely clear that treatment with burosumab is a level of magnitude better than the only other option available today (supplementation with phosphorus and calcitriol), without the potentially dangerous side-effect of kidney calcification. Paediatric patients cannot afford to wait for additional evidence, when the treatment is known to be both safe and highly effective. Any delay in access to the best available treatment—be it a matter of years, months or even weeks—reduces or even closes the window of opportunity for them to achieve the best possible health income. Children now approaching the age when bone growth ends cannot wait for additional data, since their only chance for maximising their bone growth to give them the best chance of a healthy future is right now.

The NICE HST evaluating committee acknowledged that XLH is a serious condition, that childhood is the best time for treatment, and that burosumab is more effective than standard treatment, but still concluded, in essence, that the benefits of treatment were not worth the cost. Much of the consideration, however, seems based on that treatment should stop at age 18 (since burosumab is only approved for use by children in Europe), and then, as with current treatment, symptoms would recur because there is no permanent fix to the metabolic system.

This does not take into consideration the improved starting point for a young-adult patient who has received burosumab treatment up to that point. We believe that if the paediatric patients' bones are properly mineralised and straightened during childhood, the progression of symptoms will at least be slowed, if not prevented completely. Properly mineralised bones are far less likely to require invasive corrective surgeries in childhood (and less likely to need additional surgeries later in life), followed by a lifetime of pain from non-unions and muscle weakness as a result of those paediatric surgeries.

For children, early treatment could also potentially mean that dental abscessing may not be as prevalent (many patients report having most or all of their teeth abscessing and requiring extraction or root canals by middle age, which presents a significant economic burden). In XLH, the under-mineralised dentin creates microscopic holes leading to spontaneous dental abscessing. Treatment with phosphorus and calcitriol offers only a minimal reduction in the abscesses, presumably because the blood phosphorus levels are not stable with the old treatment. With burosumab, children will have a consistently normal serum phosphorus level while their adult teeth are forming, which should lead to proper mineralisation of the teeth and much fewer spontaneous abscesses. Visiting the local dental practice is a frustrating and emotional experience no matter what, and is worse for an XLH patient needing specialised care. It's not uncommon for a patient to find, after the root canal treatment has started, that a dentist who has never before treated an XLH patient does not have the necessary tools or expertise to complete the root canal treatment, due to the unusual shape and size of the pulp chamber and root. As a result, if it's attempted by the local dentist, there’s a high chance of failure, and the crown which has cost significant money will have to be lifted and attempted once again, or the tooth may need to be extracted. In addition, locating a dental specialist for a rare disease can be time-consuming and involve substantial travel.

We also believe that your report does not sufficiently acknowledge that the current treatment (phosphorus and calcitriol) is, even in the best of circumstances, far less effective in mineralising and straightening bones than burosumab is. You do say, and we completely agree, that "The clinical experts explained that it is challenging to heal bone defects with conventional therapy, and only a few people are expected to have improvements with conventional therapy, but that burosumab is expected to provide significant bone healing." Thus, it would follow that even if children are forced to go off burosumab when their bones are fully formed, they will be in far better condition at that point than they would have been if treated by phosphorus and calcitriol.

Through our work with the patient community, we have heard many, many stories of patients who were on the current treatment (phosphorus and calcitriol), were advised to go off it at age 18 or thereabouts (because of the potential damage to kidneys), and then regressed over the next ten to twenty years. While that would likely still happen to some degree if burosumab is not ultimately approved for adults in Europe (as we believe it should be, since the need for phosphorus never goes away, and is in fact a major building block for not just bone but also for providing energy to muscles), at least patients who have had burosumab during their childhood will start off stronger and with straighter bones than if they'd only been treated with phosphorus and calcitriol.

It should be noted too that some patients do not respond well to phosphorus/calcitriol, and other patients cannot tolerate the supplements. Phosphorus supplements in the quantity needed for clinical benefit cause most people extreme gastrointestinal distress, and patients who report this say it as people who have lived with chronic bone pain for their entire life. Some will even

experience severe gastrointestinal pain from phosphorus supplements before they reach a clinically-effective level, which means that these patients cannot be on the current phosphorus/calcitriol treatment, so their only options are no treatment or burosumab.

We also believe you do not fully comprehend the nature and extent of pain experienced by XLH patients, even when they are on the current treatment (phosphorus and calcitriol). The XLH community is, I would say, not so easily fazed by pain since the disorder affects patients from birth, and consequently growing up with the chronic bone pain and aches increases their pain tolerance. Pain is simply "normal" for XLH patients, and is largely disregarded until it becomes extreme. We do not believe that this is adequately documented in the draft evaluation from NICE. Bone pain is significant in the life of a patient with XLH, since patients are frequently taking pain medication over long periods of time, and even so, some need to take time away from school, work or social activities. This pain, coupled with the chronic fatigue from low serum phosphorus that patients experience, makes living with XLH a particularly relentless and stressful experience that can lead to further physiological and emotional issues that will require treatment. Pain and fatigue tend to multiply each other, so a patient who is in pain, but not fatigued, can often push through the pain. A person with both pain and fatigue, however, does not have the energy to push on. The fatigue can also magnify a lower level of pain, depleting the energy needed to cope with the pain, and setting in motion a vicious cycle of ever-increasing pain and ever-reduced ability to cope. And patients with XLH, by virtue of the phosphorus-wasting, have both pain and fatigue built into their lives.

The report refers to burosumab as having short-term clinical benefits. We believe you meant in terms of the metabolism going back to its old phosphate-wasting ways once the burosumab is out of the system. That is not the only way of looking at the benefits however. It's pretty clear that burosumab does a better job of mineralising and straightening the bone that the current phosphorus/calcitriol treatment does, and that benefit will last, if not for a lifetime, at least decades, putting the patient in a better health state before going off burosumab.

We believe the patients who could be on burosumab as children will have optimum serum phosphorus levels over long periods of time (unlike the phosphorus/calcitriol supplements that rise and fall every few hours) ensuring quality mineralised bone and nice straight legs, arms and spines, all the way to the point of adolescence whereby their skeleton has stopped growing, their optimum height reached, and the bones as straight as possible. This could mean that those children will not require the copious amounts of limb reconstructive surgery since their legs will be already straight and their levels of bone deterioration will be less significant than if they were already bowed and deformed before going back to a state of chronic phosphorus deprivation. At the very least, bones that meet at joints at correct angles after burosumab treatment in childhood will be less prone to early-onset osteoarthritis.

We also do not believe that the evaluation has considered the impact of past injuries on a patient's well-being, along with the fear of future injuries or re-injury. Once children have had corrective limb surgery, they are forever weakened in the relevant portion of bone by the procedure. To make things worse, because of the very nature of XLH, which means not being able to mineralise quality bone, the orthopaedic fractures may take far more time to heal (years, rather than weeks), and may not heal well in the end, if it heals at all. With that in mind, returning to a productive life after surgery is yet another challenging experience. We have heard from a number of both children and adults who have injured themselves and have a fear of further injuring themselves, even sometimes suffering from compound fractures, because of a limb weakened in the course of orthopaedic surgery.

We also believe that this evaluation does not consider the mental and emotional health of paediatric patients with XLH. We cannot overstate the significance of a treatment that allows these young patients to experience a childhood more similar to that of their peers. Caregivers of paediatric patients in clinical trials have reported significant increases in their children's physical and emotional wellbeing.

In terms of the economic value of burosumab, we will be the first to admit we are not an economists. We do think, however, that you underestimate, again, the benefit of being on the best possible treatment during childhood, as compared to the really quite inadequate current treatment (phosphorus and calcitriol). You reject one aspect of the proposed economic model, which was that "nearly all people having burosumab [would be] in the healed health state by the time treatment was stopped, whereas there [would be] a distribution of people across the different health states for conventional therapy."

While we understand the full evidence for this has not yet been presented, simply because no one has been on burosumab for an entire childhood, it's quite clear, based on the better bone healing/straightening on burosumab that has already been shown to occur almost immediately upon beginning burosumab treatment, that this is going to be true.

Additionally, we believe you're conflating two issues in this discussion. One is the degree to which conventional treatment gets a patient to a "fully healed" state of good health, and the other is whether they'll STAY that way after stopping burosumab. It's pretty clear that for patients on the current phosphorus/calcitriol treatment, they NEVER get to a fully healed state. Not one of them. That needs to be compared to the logical conclusion that can be made even with current evidence, that the vast majority of burosumab patients will reach a fully healed state by the end of adolescence compared to NONE on conventional treatment. Sure, both groups will revert to phosphate-wasting if taken off treatment. But one will have a better starting point, delaying the deterioration.

We also believe you are underestimating the cost of both surgery and disability in adults with XLH, and how much could be saved by giving patients a stronger foundation during childhood. Through our work with the patient community, we're aware of the many, many patients who have had double-digits' worth of surgeries by the time they're forty! Operations done during childhood later have to be repaired or replaced or the limb must be reconstructed once again in thirties and forties. Others have knee and hip surgeries in their thirties and forties, far earlier than the general population. Patients develop spinal stenosis and spinal calcifications, requiring multiple operations in their 50s and 60s, again, far earlier than the general population.

Adults with XLH often find it hard to complete a full day of work, due to persistent pain, chronic fatigue, and mobility restrictions. Through our work with the patient community, we've heard countless stories of heartbroken patients who loved their work—as nurses, teachers, and other highly rewarding careers—but were forced to retire or go on disability living allowances a decade or more before they would have liked to stop. Or they've been dissuaded completely from a career they're passionate about, because of the physical toll it would have wrought on their weakened musculoskeletal system. That has a significant financial impact on both the patient and society in general. And these are not people who complain at the least little thing or are looking for an excuse to stay home. These are patients who are unfazed by broken bones, often untreated, and who STILL go to work or raise families or are otherwise productive members of society until it just becomes too much for them.

On behalf of the patients and carers of patients with XLH, we ask that NICE, NHS England, and

all stakeholders work together and work quickly to find a way to ensure patients will receive access in a timely manner to burosumab, a life-changing treatment that will have a substantial positive impact on the patients' ability to participate in everyday activities over a lifetime, and the quality of life for both the patients and their families. Children and young people currently living with XLH are running out of time to have a reasonably good, healthy future.

Yours sincerely,
Oliver Gardiner

XLH UK, founder and chair
XLH Network, Inc., member of the board of directors

NICE HST Burosumab for treating X-linked Hypophosphataemia [ID1151]

Has all of the relevant evidence been taken into account?

In my opinion, all the documents that were presented at the 1st evaluation held on 23rd May 2018 were considered.

I hope that Kyowa Kirin will present data from the Burosumab Phase III trail for consideration at next evaluation meeting to be held on 25th July 2018.

Are the summaries of clinical effectiveness and value for money reasonable interpretations of the evidence?

The trial data suggests that Burosumab is effective in healing rickets and improving muscle function & linear growth in children with X-linked Hypophosphataemia. My patients with X-linked Hypophosphataemia have participated in Burosumab Phase II & III trials at Royal Manchester Children's Hospital. These patients were receiving treatment with inorganic phosphate 4 to 5 times a day and Alfacalcidol once a day administered orally, prior to participating in Burosumab trials. I have observed dramatic healing of rickets in these patients. So there is no doubt that treatment with Burosumab is superior to conventional therapy in healing rickets.

However, the current cost of Burosumab is quite expensive for treating a non-fatal condition.

Are the provisional recommendations sound and a suitable basis for guidance to NHS England?

YES, but I sincerely hope that Kyowa Kirin will consider significantly reducing the cost of Burosumab, so that this medication can be used to treat children & adolescents with X-linked Hypophosphataemia.

6th July 2018

Professor Zulf Mughal
Consultant in Paediatric Bone Disorders
Honorary Clinical Professor of Child Health
Department of Paediatric Endocrinology
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Manchester
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[redacted]
Email: [redacted]

Comments on the ECD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	Registered nurse
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

I have XLH and so do my 2 children who are both adults now.

Every day I am in pain. And suffer from extreme fatigue. I have never been on any treatment as it adversely affected my blood levels of calcium and parathyroid. I have had to give up a job I loved due to tiredness and pain and also issues with my hearing.

I have had my deformities corrected at the age of 51. So that I could have knee replacements without the new knee replacements wearing out prematurely due to misalignment.

My whole life is affected by XLH and I believe that burosumab would help alleviate the suffering by reducing pain and tiredness. I'd love to be able to work full time for the next 12 years and have a better retirement but I can only manage part time work. I wake up exhausted and go to bed exhausted. There is never any relief. It affects my activities, social and work. I cannot walk far and often fall. I cannot engage in any activities that I'd like to. I have spoken to many others with XLH who have been in the trial in adults and they say they feel less tired and have less pain than they ever have in their whole lives. Many of them are far worse off than me. Please consider this drug for use in adults. It's my only hope for a better life with less pain and exhaustion. Thank you

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

To date my grandaughter has received no other medical treatment that helps her fight XLH apart from fairly radical surgery which causes as many problems as it solves and doesn't help her to grow!

I have a 12 year old grandaughter who has been receiving these injections for only a short period of time but the change in her is amazing! I find it incredible that NICE would even consider not approving this drug it is such an amazing step forward in the treatment of XLH. I understand that in the USA its use continues into adulthood.

Name	[redacted]

Role	Patient
Other role	Homemaker
Organisation	
Location	England
Conflict	n/a
Notes	

Comments on the ECD:

I think this new drug should be made available to anyone suffering from Hypophosphatemic Rickets because this disease affects your whole life considerably. For instance as a woman of 53 years of age apart from the usual expected symptoms such as short stature, awkward gait and considerable pain due to arthritis caused by deformed bones and knee joints.

I am also very deaf and have lost all my teeth. I also suffer with severe lethargy.

I was diagnosed with HR when I was about 3 and a half, I had knock knees and an awkward gait. Following diagnosis I had to wear splints at night but they were ineffective so I then had staples put into my knees which did help. During my teenage years my right femur was broken and reset.

Coming up to date I'm now in need of knee replacements in both knees and hip replacements too.

It's probably too late for me now with Burosomab although I have heard good reports from adults who have been in the trials so I remain hopeful.

However it would really benefit the children born with this disease now.

Hypophosphatemic Rickets is quite a rare disease surely prevention is better than cure. These children will grow up to have strong straight bones and hopefully won't have to be subjected to multiple surgeries, constant pain, abscesses of their teeth and possible deafness. Surely it is cost effective to prevent the damage rather than repair it.

Also the psychological aspect of this disease should be taken into consideration.

Speaking from experience children with HR are bullied in school because they walk differently and are short in stature and can't compete in sports or physical activities.

Not to mention the pain in the bones and mouth from abscesses.

Too sum up because this disease is so rare surely that makes it more cost effective, we take expensive drugs now anyway and hopefully it would mean less chance of needing multiple surgeries again saving money.

If the drug is safe let those who need it, have it, otherwise what is the point in developing and researching this disease that really is a waste of money.

Regards

[redacted]

Name	[redacted]

Role	Patient
Other role	
Organisation	
Location	United States
Conflict	No
Notes	

Comments on the ECD:

Burosumab is a miracle for me and something I have wished for my whole life. It has helped my bones become stronger and my quality of life is better, and my hope for the future has been restored. My bones are no longer deteriorating because of Burosumab.

I am a person with XLH and I was in the clinical trials for Burosumab. I have suffered all my life with XLH, a debilitating illness. I have been on Burosumab for two years and four months. My health has improved due to this treatment and it truly is a miracle. My bones had very bad osteomalacia caused by XLH. The previous treatment of phosphate/calcitriol has serious side effects and it was harming my parathyroid and was not effective in stopping bone deformities, calcifications, osteoarthrits, the need for surgeries, etc. I was deteriorating before i went on Burosumab.

I am now getting better every day. For the first time in my life, my blood phosphorous levels are normal, and my parathyroid went back to normal. My bones are getting stronger. My pain level has gone down, my need for pain medicatiob has been reduced, I no longer need to walk with a cane on a regular basis.

Please do not deny XLH patients in the UK this life changing treatment. These people need Burosumab. It has been approved in the USA and I will be continuing my treatment. Give your people the hope that I have been given, for a better, more healthy life.

Burosumab will save money in the long run, because it will help prevent the terrible bone deformities that are caused by XLH. Childrem with XLH will grow strong straight bones and will no longer need surgeries to straighten their bones. Adults with XLH will be less likely to have stress fractures and broken bones, less arthritis, less opioids, etc, with the treatment of Burosumab.

Please approve Burosumab. Thank you.

Name	[redacted]
Role	Mother of son who has XLH
Other role	Cleaner
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

I am a mother of a 3 year old boy who has been on this medication since March 2018. This medication has been improving his XLH and his life style. The previous medication wasn't working for my son. So taking this new medication away from him will be life changing and not for the better. I also suffer with XLH and the medication didn't work for me and now I am suffering and I'm only 25.

I'm really cross to think you can put a price on a children and their lives. This medication is a way of giving my son a possible normal life, also possibly stop the bullying. I got bullied because of my condition, I would hate to have my son be bullied because of his XLH and knowing that there was a medication that worked that got taken away from him.

Please reconsider.

Name	[redacted]
Role	Patient and also a carer of a child with XLH
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

The side effects for my daughter taking phosphate sandoz and alfacalcidol. My daughter also has a rare form of colitis and taking phosphate sandoz 5x a day has terrible side effects of chronic diarrhoea (causing immense distress in a 4 year old as she sometimes loses continence), nausea at times and uncomfortable stomach cramping.

It is also a battle to get her to take it 5x a day and she is now having to have a dose in the night which affects her sleep badly. To get multiple doses in a day of a medication that needs to effervesce takes planning and has a big impact on her life, emphasising numerous times a day that she is different from her peers. Despite taking this regularly, she is still plagued with bone pain, already has significant deformities that unless she receives the burosumab will almost certainly need surgical intervention. It affects her ability to run and play with friends and she frequently cries herself to sleep from pain.

For myself (also affected), the side effects are similar but I have also faced numerous problems as side effects from my treatment. On stopping it due to severe side effects, I developed un-healing stress fractures requiring intervention. I am now back on treatment but have already needed several surgeries due to numerous complications from my bony deformities. Had I had this treatment as a child, these almost certainly would not exist.

At age 35, I am awaiting significant neurosurgery next week for bony complication. I also have significant degeneration in my spine and in all my weight bearing joints due to the rickets deformity I have. I do not want the same for my daughter.

This new medication has not been recommended sadly due to cost. As a GP myself, I understand somewhat more than most about commissioning and QALYS. I fully understand that this is an expensive medication but we are talking up until age 16 when puberty ends. This treatment would only be for a small number of children each year and could literally change their lives. I as a GP have lost a lot of time off work due to surgeries and treatments.

Can I ask if reduced ability to work in adulthood has been factored into these appraisals? In addition I would also like to comment that should this appraisal not have gone down the specialist drugs route rather than the technology appraisal route

which is designed for assessing medications for chronic disease in ADULTS. I am aware of the processes involved due to familiarity with Dinituximab beta in childhood cancer and the current debates facing this medication. It worries be greatly that the suggestion currently is that burosumab will not be funded.

This is the first ever medication that could make children with XLH live an effectively normal life and the results speak for themselves in the trials. As an adult, I appreciate that treating adults may not necessarily be possible however, denying this treatment to children is effectively sentencing them to life long deformity and disability and multiple surgeries.

As a GP, I completely understand the need for rationing, but the current system used to assess these drugs was not built for children and as such is discriminatory against age. We will fight this every step of the way. As a parent who has lost a child to cancer, it is so wrong to see a treatment that is known to work be discounted effectively on cost alone.

A treatment that could give a child a normal childhood. I hope this is something you can reconsider. In the meantime my 4 year old will have to remain on regular pain killers to take the edge off the pain (they do not relieve it fully) and deformities that are increasing by the day.

A very disappointed GP.

Name	[redacted]
Role	Carer
Other role	mother
Organisation	
Location	United States
Conflict	No
Notes	
Comments on the ECD:	
Not approving this drug condemns patients to possibilities from nephrocalcinosis and kidney stones through severe arthritis and would in my opinion constitute abuse. This medicine has made SUCH an amazing difference in my daughter's life. See my daughter is a creative, funny, smart 10-year-old girl who has unfortunately been teased and bullied for being different. Not only does this medicine make it so she can grow straight without the same sorts of arthritic pains she used to have (and seems to eliminate later life complications) but it also makes it so she doesn't have to disappear from her peer group and life multiple times per day, worry constantly about forgetting to take one or if the dosage is correct this time, and most importantly just be a little girl. Burosumab has given her a LIFE.	

Name	[redacted]
Role	Patient
Other role	
Organisation	[redacted]
Location	Other
Conflict	No
Notes	
Comments on the ECD:	

I am disappointed that this drug may not be available for children as it has shown to significantly decrease the severity of symptoms and the disease progression. As an adult living with XLH I hope that children don't have to live with the surgery, pain, dental abscesses, and limited mobility that I live with on a daily basis. Not making this drug available is a big loss for many families and will cause then to be more of a burden on the countries health care system as they age.

Name	[redacted]
Role	Carer
Other role	Receptionist
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

Both myself and my two children have x linked hypophosphataemia my two children have just started the fortnightly injections burosumab at the Queens Medical Centre in Nottingham England.

I just want to say what a difference this has made to my children's lives. Having had to take the oral medication of phosphate sandoz 5 times a day previously to the injections which they have been on since 6 months of age they are now 4 and 7 years old day to day life is so much easier. We found taking the medication so frequently was a bind especially when on holiday or going out for the day having to remember to take medication with you and water and a cup to administer this. My 7 year old who is at school was often interrupted during lesson times for a teacher to administer the medication to her which was an inconvenience on both parts.

Please please please NICE consider the benefits the new injection is having on these children's lives the injection is far more accurate way of treating the symptoms of the condition. As having to also cut tablets up to give the required dose is not ideal and the odd time when a dose has been missed due the frequency of it is also not effective.

The injections I believe are having a massive impact on my children's health and there symptoms my son who has had constant mouth abscesses for a while now every few months since being on the injections seem to have put a stop to these. They also seem to be growing better too.

I understand that there are only 250 children with the condition in the UK and the cost implications are high but what costs can you put on children's health and wellbeing. Please can you take into account what a massive and positive part these injections are having on these children's lives with this very rate condition?

Thank you for your time and we wait in anticipation for a positive outcome.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	United States

Conflict	No
Notes	
Comments on the ECD:	
Current treatment does no good, the shots are our only hope.	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	United States
Conflict	No
Notes	
Comments on the ECD:	
As a patient I can't begin to describe fully what I've been through because of this disease. I've had my legs reconstructed 5 times and still have my right leg that's still out of alignment with a permanently dislocated patella. My bone quality is so bad that I'm not a candidate for replacement. The traditional treatment of oral Kphos and Calcitriol isn't helping at all except to make my parathyroid gland lose its collective mind. That puts me serious risk of surgery to remove them in order to protect my kidneys. Crysvita changes all of that. The parathyroid isn't being aggravated which protects our kidneys. It also improves our bone quality so that I can get my knee replaced so that I can maintain my mobility to finish raising my kids. I'm 48 years old. This new treatment is what we've needed for decades. It's a light at the end of a crippling tunnel. Please allow this to move forward for all patients over 1 year old including adults. If this were your family member you'd be asking the same thing. To deny anyone this treatment will be cruel. Thank you for hearing me out. All any of us want is a treatment where we've got a fair shake to live our lives as best we can. This new treatment gives us the only chance we've ever been offered.	

Name	[redacted]
Role	59 year old XLHer
Other role	
Organisation	
Location	Other
Conflict	No
Notes	
Comments on the ECD:	
The people who participated in the study are the only ones who know first hand what this does. From everything I have read from participants, they are in favour of this new treatment option. I am in favour as well. Thank you. I have XLH and am 59. I would have loved something like this.	

Name	[redacted]
Role	Patient
Other role	Medical Secretary
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	
As a lifelong sufferer of XLH having been passed the PHEX gene by my father, I struggle daily with pain, fatigue, stiffness, stress fractures, currently which are in both feet. Mobility is an extreme difficulty and despite this I continue to work. The time I have to do this has been extended to 67 years. I feel it likely I will not manage until this age as XLH is a progressive condition where all the above symptoms worsen year on year. I have been ticking off the days/weeks/months until such time as I am able to take this drug as my Rheumatologist informed me at my last consultation in May that I would be a candidate for this drug, having had my genetic testing to confirm the presence of the PHEX gene. If this drug is not to be made available to me, I will need to retire from work on the grounds of ill health which will mean I will then be forced to apply to the State to help me live. This is my personal account as an XLH sufferer as to the huge difference this drug will make to my life in my latter years.	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	
None	

Name	[redacted]
Role	Public
Other role	Retired
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	
This product is the only treatment to date that has improved my granddaughter's quality of life, other drugs available have serious detrimental side effects. Also she has undergone many operations and as well as being unpleasant for her it is also	

very expensive to the NHS.

Name	[redacted]
Role	Public
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	

With regards to the availability of this medication in the United Kingdom, I would like to bring to attention a few key points:

My partner suffers from XLH and has required multiple surgeries throughout her life (both infant and adult) to correct her posture and to attend to fractures caused by the condition.

The frequency of surgical intervention has caused my partner to develop severe allergies to almost all forms of anaesthesia (causing anaphylaxis), surgery has to be now carried out under Fentanyl and/or spinal blocks.

She currently takes calciltrol and phosphate on a regular basis, but this does not improve or sustain her condition (i.e. her bone structure continues to deteriorate).

Tramadol is required to alleviate the pain caused by the condition, but after multiple surgeries my partner is now disabled because of the condition.

The current cost of care for my partner is astronomical - surgery costs, consultation costs, dental costs, disability allowances, medication (calcitrol, phosphate, tramadol), allergy tests etc.

Dental abnormalities cause extreme pain, usually from the formation of abscesses

Myself and my partner have a 7 month old child who has inherited the condition and it will vastly improve her quality of life, if she can have access to Burosumab.

Name	[redacted]
Role	Patient
Other role	
Organisation	[redacted]
Location	Wales
Conflict	No
Notes	
Comments on the ECD:	

Both my daughter and I have the XLH condition which we are effected severely. The current medication regime was not effective in both our cases which led to prolonged and extensive limb reconstruction surgery. Phostphate causes extreme and painful abdominal cramping and diarrhoea which can make a child tolerance to taking it low. The medication does not always combat the physical symptoms of ricketts and

caused extreme anxiety in both me and my daughter which we now are medicated for.

The surgery has allowed us to continue to walk some but we live on a cocktail of pain medication to get through our day. When you take into account the lifelong cost of taking phosphate and caciterol which adults with XLH do require regardless of age old studies that are being used to decide on the future medication of XLH coupled with the cost of surgeries and secondary conditions such as depression anxiety and pain medication I can say as a sufferer that NICE are not taking into account the long term costs that can be reduced if bursumab were to be passed for NHS use.

As a committee surely you must address these issues before saying No to a drug that has the possibility of preventing additional costs long term associated to a medical condition. The UK know so little about our condition we must be look to the counties that invest into research to guide us.

Name	[redacted]
Role	Patient
Other role	[redacted]
Organisation	
Location	United States
Conflict	No
Notes	

Comments on the ECD:

A breakthrough in the treatment of X-linked Hypophosphatemia that is in short, a God send, needs to be approved and made available for patients who suffer from this disease, not only because of the huge progress in the physical wellbeing of the patients but for the good of society as a whole.

This medication has the ability to effect the number of patients who have severe complications associated with current treatments, which includes renal/kidney damage. The new medication completely illuminates the probability of kidney damage and subsequently the huge burden on medical community and the state from treatment of kidney failure. This medication also has high probability of decreasing the number of patients who need extended and ongoing treatment for complications associated with the disease process including bone joint degeneration needing surgical correction, medical devices, and lifelong pain medications.

Please consider the benefits that this drug could have on the communities that these patients are part of in addition the benefits to the patient.

Thank you for your time.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	United States
Conflict	No
Notes	

Comments on the ECD:
I am an XLH patient. Although I was diagnosed early and have taken the currently available Phosphate and Calcitriol treatment religiously my whole life, I have still required multiple surgeries and have experienced disabling pain, spinal stenosis, and dental problems as a direct result of my XLH. Since participating in the burosumab trials, my pain has been greatly reduced and my mobility has greatly increased. I've gone from severe depression and being on the verge of being unable to work to working full time happily and actually enjoying life. Yes, burosumab is expensive, but to deny this drug to children born with XLH purely due to the cost is unreasonably cruel. For children, Burosumab will mean the difference between a lifetime of pain, surgeries, tooth abscesses and disability and living a normal healthy life. For adults, Burosumab means a significant reduction in pain and increase in mobility. The improvement in quality of life is substantial. To deny Burosumab approval simply due to cost is equivalent to telling these patients "We're sorry, but your quality of life, and your child's future, is simply not worth the expense." How anyone could, in good conscience, make that decision defies explanation.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	
I was diagnosed with XLH at 6 weeks old, along with my younger sister. We inherited the condition from my mother, who was a spontaneous case and didn't get a diagnosis until she was 9 years old. My 7 month old daughter has been tested for XLH and we are awaiting the results from Guys Hospital. If my daughter does have the condition, I am extremely worried about her future without the help of the new treatment. XLH affects my life and the life of my family in many different ways. We are very short in stature, I am only 4ft6 and classed as having dwarfism. I suffer from metabolic bone disease, arthritis, hyper-mobility, severe dental issues, fatigue, muscle weakness, leg deformities, kidney issues, deafness and my mobility is impaired. My daily life is only bearable through taking Tramadol to relieve the pain, along with calcitrol and rocatrol in an attempt to keep my levels as normal as possible. The medication has never worked for me, even at the highest doses possible. Once I began weight bearing, my legs bowed and the bones began to twist. At the age of 10 I had my first surgery, which left me in full leg casts for 2 years. The surgery was unsuccessful, so since then I have continued to need surgery to simply ensure my legs were still useable. My last surgery was in 2015, when I had a [redacted] Spatial Frame put on. It has once again been unsuccessful.	

So much surgery has resulted in me developing an extreme allergy to most types of anaesthetics, to the point that it is not safe for me to be put under. I now have to have surgery whilst conscious. It is not just the physical toll a condition like this has on a person.

My mental health suffered greatly as a child. I was severely bullied and tried to take my own life on more than one occasion. I had to be removed from school for my own safety. The words midget and dwarf still haunt and sting till this day. With an emphasis on mental health nowadays, is it fair that one day my daughter could decide she doesn't want to be here anymore because of this condition?

I am completely reliant on my car, family and friends. Mobility and being able to go out by myself in public is very difficult for me. I am lucky I have a support network, many do not. I am currently receiving PIP to help me with my lifelong disability- one that would be vastly improved if I'd received the right treatment in my childhood years.

If it's simply a matter of cost... I've had countless surgeries, appointments, dental issues, medication, mental health treatment, benefits and other costs over the years.

Surely a medication that works is far better than this?!

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	

My daughter & grandson have this condition. My grandson is only 3 years old he is receiving the treatment at the moment his levels are now within the normal range.

My daughter 25 didn't have this chance of only having an injection on a fortnightly basic, she has had 3 major operation on her legs which gave her nightmares BULLYING at school, with having to take medication up to 9 times a day.

This is no life for a child.

Name	[redacted]
Role	Patient
Other role	Retired
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	

Current standard treatment for XLH has not changed in years, my grandsons (8 and 4) receive the same treatment I did as did my daughter. It is disappointing that now medical science has found that there is an alternative to Phosphate and Vitamin D supplementation which will hopefully also assist in the growth, they will not be able to benefit from it and hopefully attain a reasonable height. I reached 5 foot, my daughter 4 foot eight and I dread to think how tall the boys are going to get to, the oldest one is noticeably smaller than his peers at school. We were led to believe that this

treatment would be available in the UK for children and are extremely disappointed that it now appears it may not be.

For the children taking copious amounts of phosphate drinks through the day it is quite stressful. Teachers have to dispense to the younger ones and children do not always take the required amount due to the sheer volume of liquid. An Injection will normalise life at home and at school for children, leading to better dosage / patient compliance and monitoring of the disease and less stress for parents urging their children to drink large amounts of the medicine.

Name	[redacted]
Role	Patient
Other role	[redacted]
Organisation	[redacted]
Location	Wales
Conflict	No
Notes	
Comments on the ECD:	

I am a 55 year old XLH sufferer. Born in 1964, misdiagnosed and mistreated until I was 18. I have suffered pain, deformity and have been ostracized by society because of the effects of XLH.

Imagine walking down a busy high street with hundreds of people and only you walk like you....everyone turning and staring in horror....the polite few turn away...some laugh....some point...some throw stones or spit at you...that is my reality. No child should endure what I have been through when there is a cure available.

The cost of treated me has been astronomical in terms of money and of my wellbeing. Massive doses of Vitamin D from birth until age five, four tibial osteotomies at age eighteen, on alpha and phosphate sandoz all of my life, two femur CHAOS surgeries at 48 and 49. Numerous dental abscesses and subsequent specialist treatment. Deafness, a hearing aid. Outpatient appointments by the thousands.....I had to give up work at 48 because I could no longer cope with the pain of XLH.

My marriage broke down because my partner didn't want to be with 'an invalid'. XLH is a cruel and painful disease...little is known about it and treatment has been hit and miss....until now.

Please fund the new medicine that will give the next generation a better life. I am sure it will be cost effective in the long run. Don't sit back and let another generation of XLHers suffer as I have.

Name	[redacted]
Role	Public
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	

The patients who suffer with this condition have a very difficult and stressful life. This especially affects young children in many different ways. An example of this is when they have to take pills at regular intervals causing them embarrassment. Could this

not be solved by a simple injection.

Name	[redacted]
Role	Patient
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	

I have XLH as do both my grown up children, my mother is a spontaneous case she is in her 80's and is now totally disabled and is in constant pain. I have had numerous surgeries as have both my children, this means having a great deal of time out of school and work, the social, financial and emotional side to each person is tremendous and is ongoing though out our life.

I do not see a future for myself or my children or their future children without our health and wellbeing deteriorating. This could be changed beyond our expectations by having Burosumab.

We live in constant pain and never have the energy to live our life as we would like, turning down social and work opportunities.

My children are having to make a decision on whether to even bring another person with XLH into the world because it's not what you would want someone you love to be sentenced with.

The prescribed medications available to us at the moment do not cure or help, have bad side effects and rule our life, this is not acceptable when there is a drug which could turn all this around for all XLH patients.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	United States
Conflict	No
Notes	
Comments on the ECD:	

This is an excellent evaluation of numbers to numbers. But some math is missing.

The report lacks to detail the ratio of children with gastro problems created by Burosumab vs the problems created by phosphorous. ZERO.

The report lacks to report the level of activity the children in Burosumab have because they feel good compared to the number of children who will stay in a stroller past 6 years of age because their legs hurt. And the report lacks to recognize that the poor bone formation on children with XLH treated with current medication still causes osteomalacia and there are many other health issues that develop later in life caused by the poor bone quality.

The report fails to demonstrate that the current therapy is efficient for the treatment of XLH. The report clearly shows that the treatment with burosumab is efficient.

I am an adult with XLH, like many I stopped any treatment as an adult. My bones were damaged even if I did not know it. Eventually the effects showed up. Two knee replacements, I would not dare to walk for half a mile.

I started taking burosumab, two years later I took a vacation where I walk over 35 miles in a week. I call that success. My bones are damaged, I have bone spurs in several joints, burosumab is not going to remove that, but it will help reducing the formation of more and getting my bones stronger. If that is me as an adult, even more so on a child whose bones are still forming. Back to the numbers. The statistics say that there are 1 ever 20000 births. England has a little over 600000 births per year. That's 30 kids will be born this year with the disease. 30 kids that you have in your hands the power to get burosumab and help them obtain their full skeletal potential. And statistically speaking there should be about 600 or less children affected in UK. Are you saying that these 600 kids are not allowed to have a healthy life?

Yes it is a lot of money, but how many kids have diabetes and how much money you spend on them? For a lifetime. Are those kids with diabetes better than the kids with XLH? Are you discriminating simply because there are a minority? If there were more children perhaps the medication would be cheaper but fortunately there are just a few. But their suffering is large. The report here is longer than what it will take to write down the name of all the XLH patients.

I would say that the report totally discriminates against the minority of children with XLH, there is no alternate treatment that shows success. I demonstrated in just a sentence that burosumab represents success.

Why would you not approve it for just a population under 1000?

Name	[redacted]
Role	Patient
Other role	Patient
Organisation	
Location	
Conflict	No
Notes	

Comments on the ECD:

I am a 56 year old XLH sufferer. I was treated with high potency vit D until the age of 18. 10 years ago i was diagnosed with ossification of the posterior longitudinal ligament (attributed to my XLH) and underwent spinal surgery in an attempt to relieve pressure on my spinal cord. This was unsuccessful and resulted in quadriplegia.

I am now fully dependent and a burden on the state and my family. I have a son who is an XLH sufferer. He has been treated in the conventional way with phosphate and calcitriol, has suffered several painful surgeries to straighten his legs and I am terrified that he may end up in my situation. This new medication seems like a god send and may save patients a great deal of suffering and in the long run, a saving to the health service.

Name	[redacted]
Role	Mother
Other role	[redacted]
Organisation	

Location	England
Conflict	No
Notes	
Comments on the ECD:	
My daughter is a spontaneous case of XLH. She is currently taking phosphate sandoz 5 times per day plus alfacalcidol and vitamin D. This is a total of 2,190 treatments per year. In addition to quarterly hospital appointments with the endocrinology consultant she has blood tests every 4 weeks, sees the physiotherapist every 2 months, the rheumatologist every 2 months, sees the ophthalmologist every year, has a kidney scan every 2 years and sees the orthopaedics for fitting of orthotic inserts for her shoes every 6 months. This is a huge additional burden to the usual trials of being a teenager which puts significant pressure on our family and her siblings. Whilst being fit and active (a swimmer as it the only sport that does not give her pain) she is limited to the distance that she can walk and she struggles to run. She has constant joint and muscle pain and recently needed crutches due to tendinitis that she aggravated because she is so used to "ignoring" pain and keeping going. I have been very encouraged to read of other XLH patients who are on the Burosumab trial who have been able to drastically reduce their daily pain killers and desperately hope and look forward to my daughter having a similar outcome. Please approve this medication to dramatically improve her quality of life.	

Name	[redacted]
Role	Carer
Other role	Retired
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	
We are the grandparents of a 15 year old girl with XLH and have been closely involved with the family. We would please ask that you carefully consider allowing this treatment for her and other children with the same condition. Although she has grown up with the present treatment the discipline of the 4 hourly treatment is very hard on her and the whole family. When we have been looking after the family we notice that her energy level drops as the next treatment is due She also suffers from joint pains. Her parents are very keen for her to have this treatment as we are. We would be willing to discuss this with you.	

Name	[redacted]
Role	Public
Other role	PLEASE RECONSIDER!!!!!
Organisation	
Location	
Conflict	No
Notes	
Comments on the ECD:	
PLEASE RECONSIDER!!!	

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	England
Location	
Conflict	No
Notes	

Comments on the ECD:

My daughter already at the age of three feels self-conscious and different by being so small against her peers. Noticing and asking why she is smaller.

Why can't she keep up with the others? She isn't as mobile or can run as fast as her friends, spending far more time in a push chair and running out of energy whilst her peers carry on playing/finish sport activities. They play physical games and very quickly she is left behind and stops playing. It hurts us to see her so upset over this at such an early age.

Name	[redacted]
Role	Mother
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

My daughter is a teenager and has XLH. As a family we have found ways for her to manage and not let it dominate her childhood but it has a significant impact on what she (and us as a family) can do.

For example we cannot go on family walks as it causes too much pain for Emily. I believe that the new treatment, Burosumab will reduce her joint and muscle pain and reduce the amount of painkillers that she will have to take on a daily basis. The assumption that the benefits of taking during childhood will not be maintained if it is not approved for adult use seem to me to be incorrect. Logic tells me that if you have developed strong bones in the crucial growing years then the outcome in adulthood must be improved over having weak bones through the growing years. Furthermore, 18 years of a pain free childhood is highly significant and surely not a priviledge.

Please please please approve this for children and let them have as close to normal childhood as is medically possible.

Thank you.

Name	[redacted]
Role	
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

My comments relate to the evaluation of Burosumab as follows:-

1) As the treatment is affecting FGF23 which is basically the source of the problem, why is it assumed that it is only the rickets which will improve? Surely if phosphate levels are kept within normal limits then other manifestations would not develop either eg those associated with hypercalcaemia.

2) The standard treatment is so disruptive for the patient and family quite apart from the symptoms produced by the treatment that it seems to me that not reviewing it for 13-17 year-olds is discriminatory- or rather (as new the regimen would be so much easier on the whole family) it is discriminating against all those families who are condemned by the inadequate present treatment to a life with disability.

Time is not on the side of these children as any delay in effective treatment is likely to affect them for the rest of their lives. By the time of the next review in 3 years time the present 13-17 year- olds will be too old to benefit. It was recognised in the evaluation that this time of maximum growth is especially the time when more accurate treatment is required.

I am a retired paediatrician as well as the grandmother of a child with XLH (although there is no family history of the condition) so I have seen at first hand the effect on the child; eg pain on being encouraged to try and walk (before diagnosis), abdominal pain and diarrhoea leading to faecal incontinence, needing much persuasion to encourage her to take the nauseating medicine, missing school for numerous OP appointments, being subjected to many blood tests etc; then there is the effect on the rest of the family, especially the parents who not only had to manage the rigorous dosage regime, but had also to stay up, no matter how tired (with three younger children waking early) to give the nocturnal, dose. Her schooling was also affected as described in the evidence and parents also had to make sure she received her medication on time wherever she was and whoever she was with.

She is now already developing nephrocalcinosis and has recently had ltendinitis which I suspect may also be due to calcium deposits.

I understand the cost implications but really think that the fact that treatment which is targeted at the root of the problem rather than the “blunderbuss” treatment of trying to replace the phosphates, which are being lost through lack of reabsorption, (and which causes so many other problems) is much better for the children and young people concerned and will eventually save a lot of money at present spent on regulation of treatment with very frequent OP consultations and blood tests, scans etc. Also in the future the corrective surgery which may be needed plus the lower working capacity and hence disability payments which may be required etc., would be less of a problem and would counterbalance to a certain extent the costs as foreseen today.

It seems grossly unfair that children should be denied a near-normal life instead of ah increasingly medicalised existence when the effective treatment seems to be available - albeit at a lcost but it seems that this would be limited to about 16 years, in the first instance, rather than a lifetime .

As I understand it, those children already on Burosumab for the trial will be able to continue on it. I wonder how many youngsters are involved in the 13-17 year-old assessment, but I feel, in view of the improvements already seen in younger children, that the numbers involved should be increased to take in all those willing to take the risk on the understanding that they may be enlisted as controls.

I do hope that there will be a genuine re-think on all these aspects at the next meeting.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	

Burosumab Patient Impact Statement:

My 9 year old daughter has XLH. In her case it is spontaneous and was not passed down from her parents.

She was diagnosed before her 3rd birthday and was treated with phosphorous and an active form of vitamin D under the care of a respected paediatric endocrinologist. This increased her appetite and improved her immune response to viruses and infections. She also started to grow a little more.

With the phosphorous and Vit. D supplements her body was not able to reach the normal levels of phosphorus that her body needed to heal and function normally without putting her at risk of experiencing other debilitating side-effects. Though there were some improvement with this treatment she was still not able to walk, even short distances, without experiencing pain and discomfort. I would push her in a pram while I carried her younger brother. She would often experience sharp joint pain that would last days and prevent her from using the effected limbs (she told me recently that she remembers what piece of furniture in our home she would use to press on, in an attempt to push her elbows back in place). She would also miss school due to the pain she felt in her joints and required frequent dental work.

In an attempt to avoid calcification of the soft tissue in her body, the phosphorous supplement was given in small amounts frequently throughout the day which disturbed her activities and made her feel self-conscious.

The social and emotional impact of her XLH under the supplement treatment was also great. She began to feel depressed that she fell so far behind her peers and was often teased about her different bodily proportions.

Nearly 4 years ago, as part of a clinical trial, she began treatment with Burosumab. The change was dramatic and fast. She was initially receiving doses every 4 weeks. Within a few weeks she was complaining less about pains in her joints and was remarkably more active. Around a week before her 4 weekly dose she would start to complain a little about ankle pain. Once she was placed on the biweekly dose schedule even those complaints went away.

Today she is doing amazingly well. She is confident, happy and very active. We haven't had any dental issues in the last 2 years. She was recently elected class president and has dreams of being a political leader in the future. Most amazingly and I feel this is a true testament to how well Burosumab works on these children is that she is now a young athlete. For the last 3 years she has been competing in Women's Artistic Gymnastics, she now trains 15 hours a week and competes as part

of a squad. Gymnastics involves a combination of strength, coordination and flexibility and she is able to easily meet all three.

Burosumab is given only once every 2 weeks, hardly ever disturbing her daily activities.

These children need access to Burusomab. They should be able to run and play with confidence and without experiencing pain. They should be able to see a future without painkillers, surgery and unsuccessful dental implants.

Thank you

[redacted]

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

NICE are incorrect in denying patients with XLH treatment with Burosumab. I realise it is expensive but so is multiplied major orthopaedic surgery , time off of work and school., treatment wirh pain killers and depression which this condition causes. My whole family have XLH and all of their lives would be changed by having the new treatment. I am only able to work power time and claim benefit to make up short fall. My children cannot work at all at the moment and have been on disability related benefits for years instead of working and paying tax and national insurance and contributing to the economy.

If you had children with XLH you would approve burosumab instantly. I have watch my children in pain every day of their lives. It's heart breaking. They were bullied at school for the way they walked and could not participate in physical activities. My daughter had great lengths of time off of school with 13 operations on her legs from age 13/16. She has PTSD from the horror of these operations and all the pain. It's no fun watching your child in pain, on opiates hallucinating in terror. I had to take big chunks of time off work to care for her and our family survived on benefits at these times. It is a horrible disease which affects our whole lives from the moment we open our eyes to when we try to get comfortable enough to go to sleep.

My son had to watch his sister in pain for years and wonder if the same fate awaited him.

I have arthritis in all my joints and am exhausted all the time.

It has affected all of our hearing so makes socialising impossible.

I personally know adults and children who have been on the trials for burosumab and their lives have changed dramatically. I feel tired and in pain and unable to keep up with others my whole life from as early as I can remember.

Please reconsider your decision. The treatment of XLH causes kidney stones which my whole family have. My daughter has been admitted to hospital at least 6 times in

the last year with renal calculi. These hospital admissions cost the NHS time and money. And the treatment in pain killers and antibiotics costs money.

If we were to have the new treatment I could work more hours and both my children could probably get jobs. I hoped fir so much in their lives when they were born and it is so hard watching them become more and more depressed and lose friends who they just can't keep up with physically or financially

Please reverse your decision. It is so short sighted to base it on cost. The cost of not having burosumab is huge for every family.

Thank you for reading.

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	

I am [redacted]s mother. She is five years old. Burosumab has been life changing for the reasons above.

How do symptoms (physical and psychological) and treatments (including any surgery) from childhood affect you or your child in adult life?

- [redacted] is 5 years old. Before Burosumab treatment began in April 2018 she had a 6cm gap between her knees and both legs were very bowed. She is noticeably short for her age and suffers from pain in her legs and stomach. She isn't able to run around like her friends and struggled to walk for more than ten minutes which made normal family activities difficult to plan and sometimes impossible. [redacted] experiences pain, fatigue and dental pain. [redacted] has difficulty understanding why she is different from other children physically and had difficulty understanding why she had to take medication five times a day when she was on the conventional phosphate and calcitriol treatment. She also found it hard not to have any dairy 30 minutes before or after the phosphate. Because of the fatigue, she was finding it difficult to concentrate at school and felt sleepy most of the time impacting her education. People sometimes point and stare at her legs. My husband and I are worried that this will affect [redacted]'s self-esteem and confidence as she gets older and realises this.

For children on standard treatment (phosphate and calcitriol), what are the side effects of taking current treatment? How is that a burden for the child and your family?

- When [redacted] was on phosphate and calcitriol, she had terrible diarrhoea and bloating with pains in her stomach. She would complain that her clothing and even her car seat belt caused discomfort, she wouldn't want anything near her stomach because of the pain. As soon as we got home, she would remove her clothing as her stomach was so painful that she didn't want to

wear anything. When driving in the car, she would constantly ask how long the journey would be as she couldn't wait get out of the car seat as the belt was pushing into her sore stomach.

- When going out, we would need to ensure we had enough medicine to dose [redacted] throughout the day and also it limited what she could eat and drink as she wasn't allowed any dairy 30 minutes before or after taking her phosphate. The school would have to do three doses during the school day and I would do the other two doses in the evening. It's also a burden when [redacted] went to visit friends, stay at the childminder after school or go to holiday camp as we needed to explain all about her medication, the side effects and her fatigue. She would also need to be near a toilet when out as because of the diarrhoea, she would need to run when needing the toilet and unfortunately has had many accidents which she felt embarrassed by as she wasn't able to make it to the toilet in time and resulting in some children at school teasing her so it affected her self-esteem. She would also suffer from a red raw vagina and burning urine which was due to the phosphate.

- My husband and I both work full time but need to take emergency day's leave off work if [redacted] had a bad night or had pain so this impacted our work and also our sleeping as we would be up during the night with [redacted] when she had pain. [redacted] said that the phosphate had an unpleasant taste and sometimes we would really struggle to convince her to take it. We tried to disguise the phosphate in juice or water but she knew it was in that so wouldn't drink it. It made it hard to get her to take this five times a day and was very stressful. [redacted] would get headaches often and would mention that she felt nauseous. On occasion, she would wake up staying she couldn't feel her arm or leg, like it was numb. She had an ultrasound on her kidneys to check for Nephrocalcinosis. This was a side effect of taking the calcitriol medication.

If you have a child who is 1-12 years old and on burosumab, please explain how this treatment is currently helping in the short-term and how you expect that it will help in the long-term.

- [redacted] has grown 1cm since starting burosumab treatment on 30 April 2018. [redacted] grew only 1cm in the 12 months prior to commencing burosumab. Additionally the gap between [redacted]'s legs caused by the bowing was 6cm on 30th April 2018 and was measured at 4.5cm on 25th June 2018. This seems to indicate beyond any reasonable doubt that conventional phosphate treatment is much less effective and if access to Burosumab was withdrawn, the NHS would be condemning [redacted]'s body to a sub-standard growth and development and in future may be challenged as unethical and bad in law. Conventional treatment can still cause bone, joint and dental complications and possibly lifelong requirement of disability and housing benefit if [redacted] was unable to work at great expense to the taxpayer. Not to mention [redacted]'s possible lack of self-esteem and mental health. Burosumab seems to be repairing the damage caused by [redacted]'s condition. [redacted]'s potential as a human being would be cut so much short if access was withdrawn. How can we look at ourselves as a society and condemn someone to lifelong deformity when a cure has been presented to us? [redacted] hasn't had as much leg nor as much stomach pain since taking burosumab compared to when she was taking the phosphate. [redacted] appears to be more alert and seems to be less fatigued since being on burosumab. As the burosumab injection is

every two weeks, she is happy not to have the phosphate medication five times per day and enjoys the freedom of eating dairy at any time of day and not having to wait 30 minutes before or after her medication. She used to have her last dose of phosphate at 10.30pm at night so this would disrupt her sleep. Her legs appear to be straightening up. Her urine and blood tests showed how positively [redacted] is responding to burosumab as her levels were in the normal range and Vitamin D level was perfect. She hasn't had diarrhoea nor a raw vagina since taking burosumab. She manages to sleep through the night, most nights, because has less pain and this helps her function better and be able to concentrate at school. [redacted] seems more active and able to walk or play for longer periods of time since taking burosumab.

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	United States
Conflict	No
Notes	I am a member of the board of directors of The XLH Network, Inc., and our organization does accept funding from various pharmaceutical companies, including Ultragenyx. We are, however, an independent nonprofit organization.

Comments on the ECD:

I am writing as the mother of an eleven-year-old daughter with a spontaneous case of XLH. My daughter was diagnosed with XLH when she was 2.5 years old. She has what doctors classified as moderate symptoms: leg bowing, short stature, and dental abscesses unrelated to hygiene. My husband and I do not have the disease, so diagnosis took over six months, and once we had the diagnosis, we felt very alone in trying to determine the best means of care for our daughter. Ultimately, we traveled across the U.S. from our home in Mississippi to Yale University in Connecticut in order to get the best care possible for our daughter.

She immediately began the traditional therapy of K-Phos and calcitriol, and we did see relatively good results from this therapy because we adhered to the protocol religiously. We also, however, continued to have problems. The standard therapy did not alter our daughter's leg and joint pain. When we would travel and know that we would need to walk significant distances, we bring a stroller until our daughter was six years old simply because it was too painful for her to walk lengthy distances. The standard therapy also caused nephrocalcinosis of our daughter's kidneys within just a few years of therapy, and we had already been warned that we would need to monitor her kidney health. She also continued to have dental abscesses on the standard therapy. In addition, taking these medicines four times daily was a difficult protocol and one I worried she would not adhere to when she got older and I was unable to supervise her adherence.

In 2015, our daughter was accepted to one of the pediatric clinical trials at Yale University, and burosumab has been life changing for our family. I am not being hyperbolic when I say this. My daughter no longer experiences leg pain. In fact, she now does competitive gymnastics and practices over fifteen hours per week. Had you asked me three years ago if my child would be able to do gymnastics, I would have laughed at the idea. She is a strong girl and she always compensated for her

disease very well, but there were some things that her body simply would not allow her to do. Since she began the new therapy, however, she simply hasn't experienced the pain that she experienced on the traditional therapy. In addition, while her nephrocalcinosis has not improved, it has not gotten worse. And she has not had a dental abscess since we began the treatment.

I am a member of the board of directors of The XLH Network, Inc., so my family has had the privilege of meeting XLH families from all over the world. When my daughter first began meeting other people with XLH particularly adults she would ask me if she was going to have a life as difficult as these people. She was scared that she too would be crippled with pain and have difficulty walking across a room. It is a relief to tell her that because of this new treatment, while it is not a cure, I am confident that she will not suffer the fates of many XLH patients.

It is my hope that NICE will reverse this decision and consider the health and wellbeing of paediatric patients in the UK. My daughter would not be able to do gymnastics if she were not on this therapy. Her quality of life would not be nearly what it is now, and I want every child with XLH to have the same opportunities she has. I want them to be able to try and do all of the activities that their peers do, and I can tell you from experience that the standard therapy will not allow them to do so.

Please feel free to contact me if you have any questions, and thank you for inviting conversation from the XLH community.

Name	[redacted]
Role	NHS Professional
Other role	Nurse
Organisation	NHS
Location	England
Conflict	No
Notes	

Comments on the ECD:

Please reconsider you decision. The question is how can the NHS afford not to grant burosumab as treatment for XLH

It is the only treatment which targets the cause of XLH rather than trying to treat the symptoms.

The current treatment requires frequent monitoring in the way of blood tests, scans, major and minor surgery, doctors and nurses time and pain for the patient. My family have all had multiple operations and suffered side effects of current treatment such as kidney stones, hypercalcaemia, hyperparathyroidism, gastrointestinal effects such as diarrhoea and nausea. These all

Cost money. Lots of money.

These can all happen and have happened in my family in spite of receiving current treatment. They all took their medication on time and regularly. No missed doses or non-compliance.

Added to this the cost to the economy of people who could be in work, not able to work and claiming disability benefits. It is an enormous cost to the country.

This whole situation would be reduced by approving burosumab for children and then

in adults.

The cost to patients mental health is unknown but must be huge. Children bullied at school and underperforming as a result. Children excluded from

Certain activities and therefore isolated. These children can grow up and not be able to fulfil the careers they wish to. They will not be able to work and may be claiming disability benefits.

The EU has recommended burosumab for use in children already. We, as a forward thinking country and with one of the best health care systems in the world should be able to have access to this and help the people with XLH.

Please reconsider and approve this vital drug for people in this country.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	I am a patient but my comments are voiced as a carer of affected children, now adults, who themselves have affected children.

Comments on the ECD:

Treatment with burosumab would be cost effective as results mainly show that it is effective in healing rickets and therefore surgery and further treatment would not be required therefore saving on resources. As the cohort of affected children is small they are entitled to reach their full height and mobility potential whatever the financial cost.

Schools are not always able to provide welfare staff to supervise administration of phosphate doses through the day , leading to poor compliance

In a proportion of families more than one child is affected. This places an additional strain on the parents/carers due to the number of phosphate doses that need to be prepared and supervised throughout the day. The impact on family life with the current drug regimen can be significant.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	Wales
Conflict	No
Notes	This medication would be positively life changing for so many with this condition.

Comments on the ECD:

Having fought for testing for XLH of our eldest daughter since she was 6 months old it has been a long difficult struggle. My mum has the condition (Daughters Grandmother), as do I her mum & carer.

Our daughter is now 12years old.

She was delayed in her developmental mild stones, she was eventually referred to a community paediatrician at the local hospital.

She didn't walk until 22 months old, was very stiff, and had a wide gait. Eventually diagnosed with XLH and referred joint care in Alder Hey Liverpool & seen at 2years & 6 months old.

She was toilet trained day and night by age of 2 years 2 months.

It was recommended & advised for her to begin treatment of alfacalcidol & phosphate

Sandoz at 2 years 6 months of age.

She became incontinent of urine from then on after phosphate until 7 years old due to a rare side effect of medication causing sudden increased urine frequency day & night. As well as soiling at times from phosphate side effects on increase on dose attempts.

She is now near end of year 7 in high school, she has a toilet pass to have emergency dashes to pass urine, this making her reluctant to drink fluids throughout the day. She has had many embarrassing toileting accidents with her bowels in school, a few being in year 6 (11 years old) as you can imagine extremely embarrassing for her.

She is low in confidence anyway without the added humility of toileting issues.

She has been taking the medication for 10 years, she is now struggling to take it, makes her feel nauseas from the smell & taste of the phosphate, have tried to take it many different ways

Our daughter has been bullied from a young age with her walking waddle & short stature, being called a dwarf by fellow students, hearing adults say she's too small for high school, really has had a effect on her confidence & affected her psychologically.

She has to plan if going anywhere with friends or with school to take and carry paracetamol liquid with her to be able to try & continue with activities with her peers. She can't participate in school sponsored walks & sports day limited or stays home.

She has suffered with pain so much over the years particularly with her ankles on walking, has frequent phases where she falls over as she trips over her foot as it turns in more when tired & joints become stiffer.

As a parent & family it's heart-breaking watching her suffer, when younger ,her younger sister would get out of her pushchair so her sister could rest, I've had to carry her on my back when coming from school as she was crying with joint pain, I also suffer from same condition as her, it's a great struggle & painful trying to carry her when she can't walk any further crying with pain & stiffness , but we would do anything to help her.

She needs assistance getting in & out of the bath with her stiffness, risk of poor balance & falls.

We've discussed the burosamab medication with our daughter, she has no issue with needles & her face lit up & was very emotional & excited that there could be a chance for her to be free of the pain & stiffness, grow & keep up with her friends &

not suffer like she has. Not to take the medicine every day that makes her feel sick when she drinks & smells it.

She also expressed how she wouldn't need to panic about going to the toilet, wouldn't have to leave all her classes in school 5-10 minutes early to avoid being stampeded on or pushed by children who are all so much taller than her, as she also struggles to keep up with them. Would have strength & confidence going up & down stairs with much greater risk of falls & injuries.

Be able to go shopping without worrying about the walk from the car park into shops tiring her out & causing her pain before she even shops.

Grow & wear clothes that aren't to fit a child 3-4 years younger than her.

Name	[redacted]
Role	Patient
Other role	author
Organisation	
Location	United States
Conflict	No
Notes	I was a member of the board of directors for The XLH Network, Inc. (incorporated in the United States) for four years, and prior to that worked as a volunteer, interacting with patients on the listserv where they shared their experiences as patients and/or caretakers.

Comments on the ECD:

I am a 63-year-old patient with XLH, who had mild symptoms and no effective treatment as a child, but more severe symptoms as an adult, largely stemming from the lack of bone mineralization during childhood, plus bones that meet at odd angles in joints. I have widespread enthesopathy (spine and all joints), chronic pain, chronic fatigue, and I have had so many spontaneous dental abscesses that virtually all of my teeth have been either extracted or root canaled. I have also been active in the patient community for the past fifteen or more years, hearing from patients about their experiences.

While I'm too old to have received the current treatment (calcitriol and phosphorus), I believe that if my bones had been properly mineralized and straightened during childhood, the progression of symptoms would have at least been slowed, if not prevented completely. I have been in the clinical trial for burosumab for 2 1/2 years, and on burosumab for at least two of those years, and my enthesopathy has stabilized (not fixed, but not worsening), and the pain has decreased substantially.

One thing your report does not sufficiently acknowledge is that the old treatment (phosphorus and calcitriol) is, even in the best of circumstances, far less effective in mineralizing and straightening bones than burosumab is. You do say, "The clinical experts explained that it is challenging to heal bone defects with conventional therapy, and only a few people are expected to have improvements with conventional therapy, but that burosumab is expected to provide significant bone healing." Thus, it would follow that even if children are forced to go off burosumab when their bones are fully formed, they will be in far better condition than they would have been if treated only by phosphorus and calcitriol.

In my role with the patient community, I have heard many, many stories of patients who were on the old treatment, were forced to go off it at age 18 or thereabouts, and

then regressed over the next ten to twenty years. While that would likely still happen if burosumab is not ultimately approved for adults in Europe (as I believe it should be, since the need for phosphorus never goes away, and is in fact a major building block for not just bone but also for providing energy to muscles), at least patients who have had burosumab during their childhood will start off stronger and straighter than if they'd only been treated with phosphorus and calcitriol.

It should be noted too that some patients do not respond well at all to phosphorus/calcitriol, and other patients cannot tolerate the supplements. I am one of the latter patients. Phosphorus supplements in the quantity needed for clinical benefit cause me extreme gastrointestinal distress, and I say this as someone who has lived with chronic bone pain for my entire life. This is GI distress that goes far beyond an upset stomach to feeling like I must surely have a ruptured intestine. I have experienced a broken arm without knowing it was broken or feeling particularly bothered by it, so I'm not easily fazed by pain. The gastrointestinal pain from phosphorus supplements, even at a sub-clinically-effective level, meant that I could not be on the old phosphorus/calcitriol treatment.

The report refers to burosumab as having short-term clinical benefits. I believe you meant in terms of the metabolism going back to its old phosphate-wasting ways once the burosumab is out of the system. That is not the only way of looking at the benefits however. It's pretty clear that burosumab does a better job of mineralizing and straightening the bone than the old phosphorus/calcitriol did, and that benefit will last, if not for a lifetime, at least decades, putting the patient in a better health state before going off burosumab.

At the very least, bones that meet at joints at correct angles after burosumab treatment in childhood will be less prone to early-onset osteoarthritis, something that I and virtually all of the patients I've talked to, have experienced.

In terms of the economic value, I will be the first to admit I am not an economist. I do think, however, that your discussion has conflated two issues when you reject one aspect of the model: "nearly all people having burosumab were in the healed health state by the time treatment was stopped, whereas there was a distribution of people across the different health states for conventional therapy."

While I understand the evidence for this has not yet been presented, simply because no one has been on burosumab for an entire childhood, it's pretty clear, based on the better bone healing/straightening of burosumab, that this is going to be true.

Additionally, I believe you're conflating two issues in this discussion. One is the degree to which conventional treatment gets a patient to a "full healed" state of good health, and the other is whether they'll STAY that way after stopping burosumab. It's pretty clear that for patients on the old phosphorus/calcitriol treatment, they NEVER get to a fully healed state. Not one of them. That needs to be compared to the logical conclusion that the vast majority of burosumab patients will reach a fully healed state by the end of adolescence compared to NONE on conventional treatment. Sure, both will revert to phsophate-wasting if taken off treatment. But one will have a better starting point, delaying the deterioration.

I also believe you are underestimating the cost of both surgery and disability in adults with XLH, and how much could be saved by giving patients a stronger foundation during childhood. I have been fortunate enough, given my mild childhood symptoms, to have avoided surgery, but through my work with the patient community, I'm aware of the many, many patients who have had double-digits' worth of surgeries by the

time they're forty! Operations done during childhood later have to be repaired in thirties and forties. Others have knee and hip surgeries in their thirties and forties, far earlier than the general population. Patients develop spinal stenosis and spinal calcifications, requiring multiple operations in their 50s and 60s. In my personal experience and what I've observed among other patients, the surgeries and disability occur roughly twenty years ahead of the general population.

In my case, I was unable to work by the age of 53, and that was despite being a highly trained professional (lawyer) with a low-physical-impact job. But I could not put in a full day of work, due to persistent pain, chronic fatigue, and mobility restrictions. In my role in the patient community, I heard countless stories of heartbroken patients who loved their work -- as nurses, teachers, and other highly rewarding careers -- but were forced to retire or go on disability a decade or more before they would have liked to stop. That has a significant financial impact on both the patient and society in general. And these are not people who complain at the least little thing or are looking for an excuse to stay home. These are patients who are unfazed by broken bones, often untreated, and who STILL go to work or raise families or are otherwise productive members of society until it just becomes too much for them.

Please reconsider your decision and make this new and truly life-changing treatment available to paediatric patients (and eventually to adults). It has made a HUGE difference in my life. It came along too late to undo the structural damage (warped joints and widespread enthesopathy) that might enable me to return to a full-time job, but it has drastically reduced my chronic pain and fatigue, stabilizing the enthesopathy that no longer gets worse every year, and allowing me to enjoy a second, part-time career as a fiction author.

Name	[redacted]
Role	Carer
Other role	Programme Director
Organisation	England
Location	
Conflict	No
Notes	

Comments on the ECD:

My 15 year old daughter has a de novo case of XLH which caused her great pain, deformity and disability up to the age of 4 when it was diagnosed. She has since been on a regime of 5 phosphate doses and vitamin D every day. Whilst this has alleviated the symptoms, she is still severely impaired in terms of mobility and growth, and she still experiences significant pain almost constantly.

X-rays confirm that, while her bone structure is improved, it is still far from normal. Her biochemistry is not under control with at least one of alk phos, parathyroid or calcium/creatinine ratio being (sometimes significantly) outside the normal range. This requires frequent blood test and with unknown long term consequences. All information I have read about Burosumab suggest that it has a strongly beneficial effect on calcium / phosphate / vit D biochemistry.

I would urge you to reconsider your current recommendation as I do not think it fully considers all of the current costs of treating XLH, nor does it fully take all of the long term consequences (and therefore costs) into account.

Name	[redacted]
Role	International Advocate

Other role	[redacted]
Organisation	[redacted]
Location	
Conflict	No
Notes	
Comments on the ECD:	
The possibility for the UK to have Burosumab for XLH patients.	

Name	[redacted]
Role	Patient
Other role	[redacted]
Organisation	England
Location	
Conflict	No
Notes	
Comments on the ECD:	

How do symptoms (both physical and psychological) and treatments, including any surgery, you or your child experienced in childhood affect you or your child in adult life?

- I am a 36 year old female from Germany with XLH, which I inherited from my father and I have lived in the UK since 2002. My childhood was marked by frequent visits to orthopaedic doctors to try and solve the knocked knees I had. This was very traumatic as it made me feel different and having shoes made higher made me look different to all the other children at school. I was diagnosed with XLH when I was around 10 years old so from the age of around 3 or 4 frequent visits to the doctors found no cure. The initial treatment for XLH was the standard phosphate and calcitriol treatment five times a day.

- As a 10 year old, I found it difficult to understand the importance of taking the medication regularly and struggled with taking the tablets at the time. Due to severe knocked knees, I underwent an osteotomy on my right leg when I was 11 which meant that I spent 6 six weeks in a plaster cast from hip to toe and could not get out of bed. I had fixator rods inserted to help with the straightening of my right leg and this has been the most painful experience in my life. I missed out on school during that time and it affected how I thought about myself. After the osteotomy I then required further surgery to correct the position of my knee cap as this kept popping out and prevented me from participating in sports, walking longer distances, swimming etc.

- Since these surgeries, I am not able to kneel down properly and cannot fold my leg under to sit cross-legged. It affects my daily life as I am not able to participate in every activity sports especially are difficult and any longer physical activity is painful. I stopped receiving the standard phosphate and calcitriol treatment when I was a teenager (probably at around 15 years old). I was then told that I would only need further treatment when I was pregnant and during the menopause. When I moved to the UK I sought the help of the Royal Liverpool Hospital and I am now on standard treatment of phosphate and alfacalcidol, following the birth of my identical twin boys, who have also inherited the condition. I find that now that I am older, I am having continued dental problems, which have resulted in at least 6 root canal treatments, dental extractions and recurring random abscesses. Also, hip and joint pain is a constant daily reminder of the condition.

- So far my twin boys have not had any surgery to correct deformities as they are responding well to the Burosumab treatment under the named patient provision.

For children on standard treatment (phosphate and calcitriol), what are the side effects of taking current treatment? How is that a burden for the child and your family?

- My twin boys are 30 months old and were diagnosed with XLH when they were around 4 months old via a gene test. Since then then they were on the standard treatment of phosphate (four times a day) and alfacalcidol (once a day). This was administered via syringe and was increasingly difficult to administer as the twins got older. Both boys would try and avoid taking the medication, often resulting in crying and screaming and getting very upset at the prospect of seeing the syringe and then tasting the medication. Initially, both boys suffered with an upset stomach but over time this normalised. Having to give medication to two small babies/children was a daily challenge going out for the day required us to make up the phosphate solution in restaurants, cafes, out in the park etc. which at times was very difficult. We often had people staring at us and with the twins crying and screaming each time the medication was given to them made it worse. There is no reasoning with children that age which makes it even more difficult. Going on holiday and transporting the alfacalcidol in a cool bag or finding refrigeration opportunities was a further challenge. In short it really makes life difficult and causes upset and distress to the children and also to us as parents.

If you have a child who is 1-12 years old and on Burosumab, please explain how this treatment is currently helping in the short-term and how you expect that it will help in the long-term.

- The twins have been receiving the Burosumab treatment since April 2018 under the named patient provision at Alder Hey Hospital, Liverpool. Since the beginning of their treatment, their blood tests have shown that their phosphate levels have normalised, which was never achieved with the standard treatment received previously. The levels first normalised after the second injection so we are very happy with the progress and success of Burosumab on the twins. From a personal perspective, the twins are more relaxed, as are we as parents, as we feel that daily life is what it should be without having to worry about having to administer medication to the twins causing further distress to the children. So far, their legs are not showing any signs of bowing or knock knees so we are confident that the continued administration of Burosumab will help achieve a near normal growth in terms of height and strengthened bones without the need for corrective surgery in the future. Their quality of life is now already much improved and if I had been given that option as a child, I would have been very grateful.

In the longer term, not having to have surgery, physiotherapy and pain in adult life should be one of the main reasons for the adoption of Burosumab by the NHS. There is no price that can be put on happiness and quality of life. Yes, the treatment may be costly in comparison to standard treatment but the longer term impacts are more important.

I personally have always felt as the odd one out not only in terms of participating in sports or other physical activity, but also from an aesthetic perspective as a woman,

not being able to wear shorter dresses or certain types of shoes due to the leg deformity has been a real burden. One added consideration, is the notion of family planning and passing XLH on to my children. My husband and I discussed this on more than one occasion as to whether it would be right to potentially subject our children to the years of treatment, pain and surgery that I had to go through. We subsequently fell pregnant with twins and even before they were born, we were keen to get them tested early to give them the best chance of treatment to prevent as much leg deformity as possible.

Name	[redacted]
Role	[redacted]
Other role	England
Organisation	
Location	
Conflict	No
Notes	

Comments on the ECD:

Our son [redacted] was three and a half when he was diagnosed with XLH. The diagnosis came after 14 months of hospital visits in which his short stature, bowed legs and leg pain had been attributed to healing rickets and had effectively gone untreated. We'd never heard of this rare bone condition before but were relieved that we finally had a diagnosis that matched [redacted]'s symptoms and that we could begin to treat.

[redacted] was prescribed phosphate and calcitriol. Administering the five daily doses of phosphate was challenging and not just because of its unpleasant taste. Phosphate cannot be combined with milk which ruled out many breakfast options. The final dose of phosphate had to be given as late into the evening as possible. Ever since he was a small baby, [redacted] had woken almost nightly with severe leg pain. We would calm him, give him pain killer and settle him back to bed only to have to wake him again a couple of hours later for the final dose of phosphate. The phosphate initially upset [redacted]'s tummy and for around the first 12 months of treatment he had diarrhoea.

[redacted]'s condition and treatment affected all members of the family. Occasionally [redacted]'s two brothers would be woken by him crying in pain or because we were giving him medication. We felt unable to leave [redacted] in the care of anyone other than two close family members. We took it in turns to stay up late for the last dose of phosphate but it was often impossible to sleep through [redacted]'s protests. All of this contributed to the stress and exhaustion we felt at a time when we were still coming to terms with [redacted]'s diagnosis.

When [redacted]'s condition and medication were first explained to us by doctors at St George's Hospital we were warned that phosphate supplements can cause nephrocalcinosis and that [redacted] would need to be closely monitored for this reason. In the absence of any other treatments this seemed a risk worth taking. We were extremely hopeful about the effect treatment might have but while his condition did improve moderately, he remains very short for his age (and in comparison to his twin brother), with a pronounced bowing of the legs. We had hoped that over time [redacted] would stop waking with leg pain but this has not been the case and we have resorted to giving pain killer routinely at bedtime.

We were therefore extremely excited when Dr Cheung at Evelina hospital explained that [redacted] could take part in the trial of a new, more effective treatment for XLH.

Since beginning Burosumab at the end of April 2018 the changes in [redacted] and in family life have been extremely positive. Firstly, we're no longer tied to a continuous cycle of phosphate doses. We all sleep better now that we're not having to give [redacted] his late night dose. [redacted] can attend school trips and birthday parties without having to be pulled aside for his medication.

When [redacted] wakes in the morning he has a good appetite for breakfast and seems more alert and energetic than he did previously. He has recently started cycling and participating in the Daily Mile at school with a level of energy we would not have expected two months ago. [redacted] no longer complains that he is too tired to play in the park after school.

[redacted]'s clinical observations have also been positive in the time that he has been on Burosumab. He is growing well and his inter-condyle distance is improving. We no longer worry about him developing the serious side effects associated with phosphate supplements. We hope that in the longer term, if [redacted] were to continue to have access Burosumab, we would see greater improvements in his growth, the bowing of his legs and the amount of pain he suffers than would ever be possible with traditional treatment. We would like [redacted] to have access to the drug that will be most effective in its treatment and it is for that reason that we hope NICE will recommend Burosumab for use by the NHS in the UK.

Name	[redacted]
Role	Patient
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

I want to ask you all the decision makers (NICE) please this is a mother pleade to put this through. I worked for NHS as administrator with minimum pay because we do not have enough money to pay us more but I love my job. If in your life time you manged to change one person life for good is a great thing and feels good! please is our children and am be in future this condition may be eliminated completely because of your decision today. Yes this may sound silly but is a pleased from a painful mother. I am in a pain and you only can help me and my child Burosumab is a magic to me and my family.

I am a single mum of three and my son (last born who is now 8yrs) is a spontaneous XLH. It was something new to me and not only that is not known or clear to my local community. I must admit that this condition costs my marriage. My ex-husband could not cope or deals with it, he end up blaming me as is x linked cromozomes and refused or may be scared of being part of it. Eventually things got worse and we divorced 2016. He never attends or go to hospital appointments or asks about it. I am not blaming him but it effects of my son condition in which some people are unable to handle or deal with.

I do live in a rural area and things like this not common. I do try to educate and explain to every professional meets my son about it. I created a daily medicines diary for my son in which time, doze and signature must be recorded. Sometime we as human being forgets to give him medicine on time and effects of it is he gets very tired, unhappy and unable to concentrate.

Furthermore while he was on medication, school and choir trips (my children sing in our local choir) is difficult if I cannot go with them. He misses sometime if no adult able to give him medicine or if the school are unable to provide a cooler to carry his medicine.

Things like when we go on holiday I have to make sure the room has fridge to store his medicines and if we are going abroad by flight becomes more harder because on a checking desk me with liquids and lots of ice cubes I get pulled aside to explain to them the reasons of caring all the liquids. I am sure we are ll aware of Airport security with liquids. This causes us become the last one to board the plane and with 3 children, one on wheel chair it cannot get more harder and frustrating.

Now I do not have to worry at all if we are going on holiday. I feel free so does my son and his sibling.

Burosumab is brilliant thing and it has already changed our living and life in general. My son is able to go to any school or choir trips without me or go to friends house for hours without thinking of medication.

Since he started Burosumab nearly a month now out life has been transformed. No more worrying about medicine, eating or any milk products. He is doing very well himself and a very happy boy. I feel like I got my boy back and our life in general.

I can write a book about this but it has been a life changing for us! no doubt and I could not ask for more other than thanking those who have been working day and night on this MAGIC treatments which transform human life like us.

Thank you from my heart.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

As a 2nd generation XLH sufferer with 2 boys who both inherited the condition I can say from first-hand experience the leg pain suffered as a child was one of the most frustrating parts of growing up along with the regular hospital visits (missed school sessions), I was surprised to find out that the treatment had not progressed within 30 years and that my children are currently being treated with the same Phosphate Sandoz and Alphacalcidol. Having learnt so much more about the condition through my sons ongoing hospital visits I understand that they will likely suffer more severe effects of the condition just because they are male and that when they are grown and have children of their own they will inevitably pass the condition on to any girls they have.

I recall being picked on as a child for the way that walked and ran (the characteristic waddling gait) which both my boys have. I have concerns that my boys will suffer the same bullying that I did at school and worry for the long term mental health of them, as the effects of bullying are lifelong!

I am only 4ft 9 in height and as my boys are both on the exact same treatment I suspect that if they continue on the same treatment they will also not achieve a final height above 5ft which will again be a knock to any confidence and can have a negative impact on what they choose to do in life.

Their current treatment involves taking medicine several times throughout the school day making it obvious to other children in my sons class that he has a medical condition adding to the fact that he is much shorter than his classmates along with the waddle makes him an easy target for bullies again.

The new treatment would make it less obvious to classmates, remove responsibility from teachers and other care givers to administer the correct dosage and give all children suffering the condition a better chance of reaching a normal/average height and I believe it may be of benefit in later life as I was diagnosed at just 33 years of age with arthritis in my knees.

XLH is a lifelong condition which brings pain to everyone who suffers it, whilst there is no cure, the new treatment has massive potential to improve the lives of all going forward, treating the cause of the phosphate wasting and preventing the symptoms of Rickets has got to be an improvement to the long term health of patients with the condition.

Name	[redacted]
Role	Carer
Other role	Carer
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

Overview

My son [redacted] is almost 11 years old. His was born full term and a healthy baby. He was very small but it wasn't until he started walking at 9 months old that this was really noticed.

He was taken to the GP and referred and at 18 months old he received his formal diagnosis of XLH (Ricketts).

As a family this was something that had not been heard of in the current day and my understanding of it was then associated in war times with children who were malnourished.

Medication

The diagnosis meant that [redacted] was then prescribed Phosphate Sandoz and alfacalcidol.

This was a very difficult to administer due to the taste of it and [redacted] being only 2, did not understand that this was medication that he was so reliant on. As a mother it was quite the opposite. This medication gave [redacted] constant Diarrhoea and due to him still being in a nappy at that age, this meant that sometimes it made his bum sore. Even when [redacted] was then out of nappies this caused a problem especially

when being out of this house when he would mess himself.

The diarrhoea lasted for around two years before [redacted]'s body finally adapted to the medication.

The medication is administered 4 - 5 times a day. This means that this is administered once a day at school during the school week.

On the current medication you have to remember to order it from the chemist in time before running out of the pervious batch. You then have to remember to take the medication to school and then also remembering to administer the medication at the allocated times when at home. There have been times when this has been forgotten and this causes me massive anxiety as I know how important this is. [redacted] also spends time with his father who makes a habit of forgetting to administer the medication and this has meant that [redacted] has gone some days without the required medication. A very stressful situation.

Dental difficulties

[redacted] had his first tooth removed due to a dental abscess when he was just 2 years old. This was a very traumatising experience for him and me and it was only then that we discovered that the condition has also affected his teeth. He then went onto to eventually have all of his baby teeth removed due to spontaneous abscesses. Each occasion was very traumatic for [redacted] and his parents.

[redacted] remains under the care of a paediatric dentist and is still receiving treatment in relation to his adult teeth. He currently only has 12 teeth and all are covered in a protective coating with the 4 molars he has covered in silver crowns. This is in an attempt to save the adult teeth from infection and extraction.

The future for [redacted]'s teeth is still unclear and it may result in him wearing veneers to replace any lost adult teeth.

Surgery

To date [redacted] has had numerous surgeries, some being major procedures on his legs. This was in an attempt to correct the bowing caused due to his condition.

He has had surgery on both legs on the Tibia and Fibula to correct bowing. This meant that he was the in plaster cast on both legs and unable to weight bear or get wet for 6 weeks. This was a massive disruption to normal daily routine and 24 hour care was needed to manage the pain he was in due to the surgery.

He then had reconstructive surgery on both hips due to the incorrect positon of them in is pelvis. This was the worst of all the procedures due to the amount of pain he was in after the surgery and the care that was required for the weeks after. Due to the surgery being on the hips and no plaster cast being used to hold him in place, the lifting him had to be done in a specific way to ensure minimal movement and to reduce the amount of pain he was in when being moved.

This is a very distressing time for a parent and it was one of the most stressful times of my life to date. A lot of planning and preparation goes into these procedures from a parent's point of view. C As a full time police officer mother this was a very stressful time for me due to the nature of the surgeries and the aftercare that was then required. I was trying to maintain going to work and being able to care for [redacted] as

best as possible. Unfortunately the pressure got too much and I was forced to take time away from work due to stress, something that has gone on to impact my sickness records with my employer. This had a massive impact on my family and other children.

After this surgery at a review with the consultant it was then discovered that [redacted] was displaying the wind swept positon as opposed to the usual bowing that he had displayed previously. This meant that his knees in particular the left knee were starting to turn in towards each other. A further procedure was then planned and this was to insert a growth plate into the left knee to try and force the bone to grow upright instead of the way it was going (inwards).

This procedure took place and compared to the previous two this was a simple procedure with minimal aftercare. [redacted] was able to weight bear as soon as he felt able and the incision site was a small area on his knee.

Unfortunately [redacted] contracted and infection in the site and was then re-admitted to hospital a few weeks after the surgery. Initially a further surgery was planned to remove the infection but on closer examination it was decided that [redacted] could receive antibiotics intravenously during a short stay in hospital.

This meant further disruption to my work and our home life and also further disruption to [redacted]'s school attendance.

Recently in October 2017 it was shown that the procedure on [redacted]s left knee had not had the desired affect due to the severity of his condition. The decision was made to remove the growth plate along with the metal work that was in [redacted]s hips (this was due to be removed anyway).

Growth

[redacted] is an 11 year old boy who is currently 114.5cm in height; this is the average height of a 5 year old child. [redacted] was born at 47.5 cm in length. It is evident that his growth has been very very slow throughout his life so far. [redacted] has a 4 year old brother who is almost 100 cm in height.

Psychological

Since [redacted] has been at junior school the impact of his condition on his life has affected him psychological and his behaviour has changed drastically. [redacted] feels inferior to his peers and is constantly making the wrong decisions in an attempt to fit in and be accepted. He has a small circle of close friends but will not venture away from this through fear of being bullied because of his size. Even with the few friends he does have he still feels the need to try and prove himself to compensate for his size.

[redacted] has been having counselling sessions since December 2017, a service we had access to via his consultant. These sessions have helped him manage some of the anger he has but his behaviour has not improved. He struggles at school due to time missed and being burdened by worries regarding his future and how it looks.

His legs are still deformed and are now covered in scars. As an adult I look at him and feel very proud of how he has handled the things life has thrown at him so far but as an 11 year old boy who is approaching puberty, the way he looks is like the end of the world and I would be silly to think that this will not affect him mentally somehow.

Evaluation

We have recently been seen by the surgeon who conducted [redacted]'s last two operations. We agree in the view that his deformities are worse and [redacted] has now been referred to Great Ormond Street hospital to see a specialist in this field.

[redacted] remains under the care of Mike HARRISON (Dentist) and Dr Moira CHEUNG (consultant).

Burosumab

[redacted] has been taking Burosumab via injection every two weeks for the last 11 weeks. [redacted] aged 11 is one of the eldest patients taking part in the current trial. [redacted] has been fortunate to have had little to no pain as a result of his condition so this is not something that I can comment on. One thing I can say is that [redacted] growth has rocketed. He is currently growing at a rate of around 1 cm every two weeks. This is almost unheard off and has massively improved our confidence in his future. Consultants have also seen a slight improvement in the width of gap between [redacted]s ankles, indicating that his legs could be starting to straighten out. Although I am aware this is very early days on this drug. I have not seen improvements like this for him in many years.

The convenience of taking this new drug is also a massive improvement and has alleviated all anxieties I had about him getting the necessary medication when he should be. This was he can have the injection and then forget about it again for another two weeks. Also because the medication is being administered by a nurse at home, I have someone else to rely on in relation to this and the responsibility is not all on me. I feel more supported now than ever before and although I have had the consultants to call on in the past I feel like I can address any concerns I have via the nurse who I will now see every two weeks.

Having been diagnosed at 18 months we have experienced many different consultants, and medication changes in relation to dose increase or decrease, surgeries and not seen an improvement of this level in all those years. This is the most positive I have felt about [redacted]'s future.

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	
Hi, Our daughter has recently been diagnosed with XLH at the age of 2.5, feel like our world has been turned upside down, Daughter currently on Phosphate sandoz 5 times a day & Alfacalcidol drops which she really hates taking & is really distressing for us all, interrupting with our daily lifes, her appetite has gone downhill. I've done a lot of research on people who have been lucky enough to get to trial this drug with fantastic results, & understand that quality of life has improved dramatically as it targets the underlying problem, not like the Phosphat sandoz which is a poor	

substitute. Please please please change your minds for these poor people with this rare disease

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

My husband and I are legal guardians to our 3-year-old grandson whom also is suffering from XLH

[redacted] is very short in stature his legs are extremely bowed and his head is over large. He has just had to have some teeth removed and all the remaining stainless steel coated to help preserve them for as long as possible. That procedure alone has come at a huge cost to the NHS

In himself at the moment [redacted] is oblivious to his differences. He is mobile but stepping up and down he has difficulty with. He approaches steps via a hip movement rather than a knee movement.

What the future holds for him we are unsure He had been accepted on the clinical trial for BUROSUMAB but was randomised to stay on existing medication of phosphate sandoz and alpha calcidol Vit D medication.

We were given a schedule to start the new drug after his week 64 assessment which was on the 26th June 2018.

We were so excited that he would start the new medication to help him in the future as he approaches school age.

This is our major worry. We have already gone through all this with [redacted]s's mother who also had XLH she is now 26 and sadly unable to look after her own son as she is a drug addict.

When she was growing up at school she was bullied by her piers her legs were badly bowed She was on the same medication as [redacted] Phosphate Sandoz and alpha calcidol.

She was under the best consultant at St Marys hospital Manchester. We made her have her medication religiously.

We made sure she attended every hospital appointment as we are doing with her son to our cost of not attending work, loosing money .It was a full days time off as the hospital was 40 miles away and she also missed full days off school , missing out on valuable education.

She was a very bright girl but missed lots of school, her disfigurement drew attention to herself. When you are a teenage girl you care what you look like and what people think of you so that you fit in. She started to rebel and refusing medication around age 13/14

Sadly, she was picked on and bullied.

She ended up making friendship groups with the wrong crowds just for acceptance.

She has had numerous counselling sessions and terms in rehabilitation, the last term where she met [redacted]s father and she got pregnant. He is a still using drug addict and that is why social services got involved and the courts awarded us special Guardianship for poor [redacted].

This New drug must be put on to the NHS register I would hate another generation of children to suffer any more like our daughter did

Now [redacted] doesn't have his mum and he also has the stigma that his parents are drug addicts he's looked after by his granny and grandad and his body is disfigured!!!!!

I fear for his future both Physically and mentally

Totally understand the financial implications. The drug company must reduce the cost

But think how much public money our family alone has used in last few years NOT by choice.

Dental work in patient and out patient

Surgeons

Paediatricians

nurses

hospital stays

rehab residences

psychiatric help / councelling

social services

courts

court orders

solicitors/ Barristers

health visitors

children centres for supervised contact

THE LIST GOES ON AND ON.....

Yours Sincerely

[redacted]

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

My husband has XLH and has been treated since he was 18 months old and has passed XLH onto our 2 year old daughter. He had many surgical operations throughout his childhood including Bilateral Oesteotomies at St. Thomas, removal of growth plates bilateral tib and fib and surgical removal of baby teeth. Over the last 10 years I have seen my husband struggle with everyday life due to poor mobility and have numerous dental procedures and abscesses due to his condition, so much so that he wants all of his teeth taken out and swapped for dentures as his jaw is too weak for implants. As a parent I cannot help but see that this will one day be our daughter struggling to get out of bed in a morning, struggling to achieve simple physical tasks, struggle to play and care for her own children and be in pain 24/7.

Whilst our daughter is only 2 years old, been on standard treatment since she was 5 weeks old and been monitored every 2-3 months, she already mimics the skeletal structure of my husband; surely a sign that the standard treatment is not good enough. Our daughter loves running around, climbing and dancing, just like a typical toddler. She is too young understand XLH or to tell us if/when she is in pain due to XLH, however I have noticed more recently that even on a short walk she begs to be carried. I'm taking this as a sign of her being in pain and it breaks my heart.

Our daughter happily takes her phosphate and calcitriol everyday. In fact, she likes the phosphate so much that she gets very upset when we have to take it away from her so that the dosage can be spread throughout the day. When our daughter spends the day with family / friends / nursery we have to ensure they remember to give her the phosphate something that can be easily forgotten if it's not common practice. It can be difficult to keep the calcitriol cold when travelling to visit family / friends for a weekend or driving for hours to go on holiday â€“ we are yet to go abroad with the medication but I imagine this too would not be easy. There are also times when the calcitriol drops are not fully taken i.e. the drops get put in her milk but she doesn't finish all the milk.

Just today I have received the latest clinic letter and it had different changes to her medication than the consultant had told me on the phone 5 days prior. After double checking with the consultant, the lower dosage of calcitriol was correct and so for 5 days she had been given 50% more than she should have been getting. It seems to me that there is a lot more room for human error with the standard treatment and it is not overly effective. In just 3 months, the bowing in her legs has increased by 1cm.

I am really disappointed with the first stage recommendation that burosumab will be rejected in the UK mainly due to cost. How can you put a price on a child growing up not being in constant pain, not needing corrective surgical procedures, not being stigmatised or bullied throughout childhood for having a genetic disfigurement? I am yet to see the psychological damage the standard treatment may cause if burosumab is rejected in October and I really hope you see the massive benefit the new treatment will give to those affected. The online XLH support groups have already expressed the fantastic results their children have had when they have received

burosumab. How is it fair that children in America or Europe can benefit from the new treatment but because we live in the UK my child is not worthy of having a happier life?

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	Child's father.

Comments on the ECD:

I am writing on behalf of my 4 year old daughter who has XLH. I believe the refusal to treat children with this condition with burosumab is discriminatory towards individuals with an inherited condition, and given the success in trials internationally, is consuming children born with this condition here in the UK to. At best, second rate care.

My daughter requires medications 5 times a day, which is very hard to administer, resulting in needing to wake the child from sleep, and results in many medication side effects, namely gastrointestinal upset. Despite this she already has had delayed walking requiring (at cost to the NHS) physiotherapy and orthotic input, and chronic bone pain.

She now has orthopaedic deformities of her legs (which with burosumab would have been prevented and with treatment even now may resolve) which could well result in future surgical interventions and possible employment restrictions. I have seen first-hand the physical and employment limitations my daughter's mother, who also suffers from XLH endures. The financial costs of not treating children with burosumab over years (both directly from clinical care and possible reduced income) may well exceed the costs of the drug over a of period of years. As such I feel the decision by NICE not to approve burosumab is not only ethically wrong given the suffering these children endure (and I talk as a primary care physician who is fully aware of the importance of clinical rationing) but I feel there is a strong argument that it is not a fiscally responsible decision either, given the above.

Name	[redacted]
Role	Local government professional
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

The condition as meant I have had 5 surgeries so far when i was 19yrs to make my legs straight and to take pressure off my hips and knees. I am now 37yrs and need hip replacements and have cartildge problems with my knees- looks like they need replacing too. I get daily aches and pains in my bones and joints- i have limited movement and unable to run, horse ride etc

I have a 2 yr old on phospate and alpha- this is required 4x a day, tastes horrible and causes her to have very loose bowels. When i took it and my elder children it caused calfication of the kidneys, diahrea and we continued to have regaular aches and pains require meds and stopping us from taking part in activities.

I have a 12yr old boy on trail (since beginning)drug which has transformed his lif! no aches and pains, had no side effects and has now made his legs straight and his grown more. He is much nire mobile, happier and social! He will not require any surgries.

I have a 13 yr old daughter also been on trial drug since it began and had has also transformed her life! Shes pain free, more happy & social, no side effects, now straight legs so doesn't require surgeries.

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	
My children, currently 12 & 13 have been taking burosumab for the last 3 years. My daughter (13) has no visible signs of XLH, while my son has some visible signs but is likely to be as tall as me (I am not affected by the condition). Neither of these children are going to require surgery later in life so they will not cost the NHS for knee, hip or other operations as a result of their inherited XLH. They will not have calcification of their kidneys as a result of the archaic treatment that they were on previously (the same treatment that their 2 year old sister is on right NOW) . Please please please - these kids need to be treated with the best option for them - you need to come to an agreement with the company that have spent resource on developing this treatment all with the unwavering support of GOSH and people like us. We have all worked so hard - the kids have worked so hard.	

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	
None	

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	United States
Conflict	No
Notes	
Comments on the ECD:	
People with XLH have waited for. A very long time for a treatment for their condition. Living with XLH is challenging, painful and difficult. Please do not deny this life changing treatment to those who need it. I have XLH And live in the USA and am so fortunate to be on this medication. It is looking like we will be moving next summer	

for my husband's job. Please don't deny this drug as I will not be able to continue taking it once we move. Talk to people who live with this rare disease and have compassion and approve this new drug!

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Patient
Conflict	No
Notes	
Comments on the ECD:	

I am an Australian and was born with XLH and diagnosed at the age of 5. I am a spontaneous case, with all my living relatives at the time of diagnoses tested. I have had 2 children, one with XLH and one without XLH.

The physical and psychological affects this rare genetic condition has had on my life and the lives of my family have been challenging and exhausting.

Some of the symptoms of this disorder are short stature, limb deformities, waddling gait, spontaneous tooth abscesses, arthritis, muscle pain & weakness, bone & joint pain, spontaneous bone fractures, joint replacements, hearing loss, vertigo, hyper-mobility of joints, compromised immunity and fatigue. The treatment that has been used over the last 40 years is activate vitamin D (calcitriol) and oral phosphate supplements, although some degree of skeletal improvement is seen with this approach, frequent monitoring is necessary because of the potential adverse effects of secondary hyperparathyroidism, hypercalcemia, and nephrocalcinosis. The complications of XLH frequently observed during the adult course of disease include enthesopathy and osteophytes (bone spurs). The most commonly affected sites include the knees, ankles and spine, and they have occurred irrespective of exposure to conventional therapy. A newly approved treatment by the Food and Drug Administration (FDA) on 17th April 2018, known as Crysvita (Burosumab) has shown marked improvement in symptoms and quality of life. Burosumab is a monoclonal antibody that binds with the excessive Fibroblast Growth Factor 23 to reduce phosphate-wasting and improve vitamin D metabolism. One of the researchers of XLH found, By targeting this mechanism Crysvita leads to sustained improvements in phosphate metabolism with concurrent repair of the skeleton, even after prior treatment with conventional approaches. Most importantly, the dosing regimen for Crysvita is far less burdensome than for currently available therapies and should be readily acceptable by families. I expect it to revolutionise the care of patients with XLH (Tom Carpenter, M.D.)

As an XLH patient this kind of medication would be life changing, and trials have proven there are less side effects than the traditional medication and a higher rate of improvement in symptoms of this debilitating life long condition.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	

As a relative of a child eligible to benefit from burosumab, I would like to express my huge concerns that it has been concluded that the benefits of treatment are not worth the cost. XLH is a serious condition and as childhood is the best time for treatment, the drug should be made available in order that as many children as possible can benefit, both in the short-term and the long-term

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

I have put carer as my role above as my son and wife have XLH. That seemed to be the best category for me of those choices given.

Dear NICE,

I am writing to ask that you reconsider supporting funding for Crysvita (burosumab) for the treatment of X-linked hypophosphataemic rickets (XLH).

My son and wife have XLH. As you know treatment for XLH has remained the same for 4 decades oral phosphate solution. Whilst this helps it does not fully correct the skeletal deformity, short stature, and metabolic and endocrine abnormalities patients face. Phosphate treatment also often leads to side effects including gastrointestinal (GI) problems and nephrocalcinosis.

My wife was diagnosed as a child, age 9, and received phosphate, but with limited benefit; she still has daily joint stiffness and knee pain. At the time of her treatment she experienced GI side effects with phosphate, which caused her considerable psychological stress, including daily panic attacks, which meant that she missed several months of school and was anxious about travelling. This lead to her having to reduce and eventually stop phosphate treatment by age 16 due to an inability to continue tolerating it.

My son, age 6, was diagnosed with XLH through genetic testing of his cord blood and so has received treatment from shortly after birth. Despite early and intensive intervention (phosphate every 4 hours, day and night) with close clinical supervision, he has growth problems and leg bowing that give him pain and affect his ability to walk and run. He also has craniosynostosis and is currently being investigated for possible raised intracranial pressure. The intensive treatment has impacted his social life as, in addition to his physical limitations, we need to make sure that he can receive his medication every 4 hours. We are also concerned about how the psychological impact the growth abnormalities he is experiencing with XLH will impact him in later life particularly his height and ability to do sports.

We were very excited to hear about the new treatment option for XLH (burosumab) that specifically targets the underlying pathophysiology of XLH. We are delighted that my son has been able to receive burosumab as part of a study at the Evelina Hospital, London. He has received burosumab for 9 weeks now and has tolerated the medicine very well. He no longer needs phosphate day and night which is a great relief, particularly for my wife and me in that we no longer have to get up at 4am every day to give him a dose â€“ a significant previous burden. He is also no longer

exposed to the adverse effects that phosphate treatment brings. Importantly the bowing in his legs and his height have improved (He has moved up 1 percentile in height already), which is likely to mean that he will not require the corrective surgery that was planned prior to him receiving burosumab treatment. His leg bowing occurred during treatment with phosphate, despite very close clinical monitoring and treatment and despite normalisation of alkaline phosphatase levels, so the fact that burosumab is already providing a physical improvement so early on in treatment demonstrates a marked advantage for him with the new therapy. His blood phosphate and alkaline phosphatase levels are in the normal range with burosumab and his risk of nephrocalcinosis is reduced meaning that his kidneys are at less risk of damaging calcium deposits. We would very much like him to be able to continue this beneficial treatment.

Recent clinical study results (Carpenter T, et al. N Engl J Med 2018;378:1987â€“98) which evaluated the effect of burosumab in children with XLH show effective and persistent reduction in rickets severity and pain together with improvements in physical ability and height. I hope that the growing clinical evidence, including that currently being collected as part of the study my son is part of, will help to communicate the value that burosumab can give to people with this rare and debilitating condition.

In summary I ask that you consider:

The growing benefits burosumab shows in clinical studies

The high financial cost of corrective surgery and post-operative care for issues including leg bowing and surgery for possible cranial pressure problems due to impairments to skull growth, on standard phosphate treatment

The cost of very frequent treatment with phosphate solution and associated general care due to suboptimal normalisation of bone growth

The difficulty in providing phosphate treatment every 4 hours. It can give gastrointestinal problems and means that as a parent you never get a full night's sleep as you must give a dose in the middle of the night. This is a significant burden for a family

The pain that can be alleviated with this new treatment

The known and unknown clinical benefits that maybe provided through correction of metabolic and endocrine abnormalities including hypercalciuria, nephrocalcinosis and hyperparathyroidism with burosumab.

The social and psychological benefits that an improved treatment brings for patients with XLH who have seen no alternative therapy options in decades.

Thank you for taking the time to read this letter. Please may we not wait until it is too late for those children who could currently benefit from this therapy.

Kind regards,

[redacted]

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	Other
Conflict	No
Notes	

Comments on the ECD:

I am a parent of a child with XLH. Our child currently receives 6 doses of phosphorus, throughout his waking hours. It is an inconvenient treatment that does not address the cause of the phosphate wasting, which is hormonal. With one dose of burosumab a fortnight, his body will stop wasting phosphorus and his skeleton will finally begin to heal. This is a breakthrough treatment which will improve the quality of my son's life.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	United States
Conflict	No
Notes	

Comments on the ECD:

Comment for Burosumab for treating X-linked hypophosphataemia

Dear Department of Health and Social Care, National Institute for Health and Care Excellence (NICE) ,

I would like to make a comment on the use of Burosumab as a treatment for X-Linked Hypophophataemia (XLH)

I am a typical adult with XLH and I have suffered physically and financially as an adult with this disease. If Burosumab would have been available for me as a child, much if not all of the cost and suffering may have been alleviated for me.

I am a 61 year old female with XLH. I would like to give a run down of how this disease has impacted me physically and financially as an adult. The treatment I received as a child was massive doses of vitamin D and phosphorus supplementation. At this stage in my life I am having many more problems than I had as a child and the costs have been astronomical. If I would have been able to have this treatment as a child, I am convinced I would not be suffering as much as I am now, along with having the financial burden that goes along with all treatments I has endured.

As an adult I started to support my dentist in my early twenties. Last time I saw my dentist he commented that I only have 6 more teeth that don't have root canals. He commented that I have been a great source of income for him. I had to pay cash for all those tooth treatments because I live in the USA which doesn't cover the cost of dental care. Todays costs for each tooth is $5000 (root canals and caps). If you multiply todays cost by 26 (the teeth that have been treated), I needed a second job just to support my teeth. To think that Using Burosumab may have allowed for proper mineralization of my teeth. This alone makes me advocate for Burosumab. You can't imagine how much suffering I have endured with each tooth abscess.

Next thing that started to happen to me as an adult is calcification of the cartilage and development of osteoarthritis. This turns out to be a very expensive disease. As a result I have had many surgical procedures, taking bone spurs out of both ankles, two knee replacements, and two hip replacements. Here in the US each of these surgery's cost $35 000. I am also a frequent flyer at the local physical therapy clinic. I have had extensive PT treatment for hands, elbows, feet, knees, hips, and I suppose my back will be next (knock on wood).

Another complication is hyperparathyroidism (Tournis ST1 2005). There seems to be a link between the phosphorus treatment and hyperparathyroidism. I have just had my second surgery for this complication. The first surgery was $28 000. And the second was just done last week, and I'm not sure what it costs yet.

At 61 I have now encountered the trifecta of bone degradation, menopause, XLH, and hyperparathyroidism. My orthopedist now tells me I will need to have to have plates put into my legs to support my crumbling bones. I can't help thinking how Burosumab may have modified the XLH, and the treatments side effect of hyperparathyroidism. For me the costs just continues.

My point is that, I am probably a typical example of what it costs as an adult with XLH. Treating the children with Burosumab may in fact alleviate many of the costs and suffering I have described. It seems to make economic sense for the future to treat children using Burosumab instead of phosphorus and Vit-D. I estimate over my adult life I have spent more than $300 000 on health care related to XLH. I feel it's expensive not to provide the best posable treatment for children, and adults with XLH.

References

Tournis ST1, Giannikou PV, Paspati IN, Katsalira EA, Voskaki IC, Lyritis GP. 2005. "Co-existence of X-linked hypophosphatemic rickets (XLH) and primary hyperparathyroidism: case report and review of the literature." J Musculoskelet Neuronal Interact. 2005 Jun;5(2):150-4. 150-4.

Name	[redacted]
Role	Grand Mother
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

My grand-daughter has x- linked Hypophosphataemia. She has been part of the trial for Burosumab and what a difference it made not only in terms of her health but also quality of life. Previously she was treated by constantly drinking a solution made with phosphate. Prior to the drug she was often in pain and had days where she could not stand due to the pain and she was not able to go to school or play. She was also teased by other children who would ask why was her had so big. Since she has been on the trial for this new drug she has been growing and is a normal happy child. She is very active doing competitive gymnastics, dancing classes is excelling at school and her confidence has improved .She is no longer teased as she is now growing in proportion. Previously (before the Burosumab) she use to get very tired and her growth was poor.

Another worrying factor was the side effect of the old treatment and implications for health issues in the future. Implications not only on the health of these children but also financial costs due to treatments latter in life. It is also well known the pain that these patients suffer during their life time. This is something that I observed with my granddaughter. At the start of the trial she was on a lower dose of the drug and usually a week before the next injection she would start complaining of pain. As the dose increased this has no longer been an issue.

For the reasons above I hope that this drug that has made such a difference not only in the life of my granddaughter but also her parents is approved by NICE.

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

Comments are given on behalf of my 15 year old daughter who has the condition:

the physical symptoms manifested themselves when she was at primary school and were so severe that she was barely able to move around the school, struggled to get up and down the stairs and obviously was not able to participate in school sports and activities. She has had to take many days off school to attend hospital appointments. When she was in her second year of secondary school she had to miss two weeks off school for surgery on her knees. Afterwards she was on crutches for several weeks, which made school extremely difficult and painful. It had quite an impact on the results of her end of year exams. She still cannot participate in sports requiring her to run and is nervous about activities which will require her to be mobile.

The physical symptoms are on going despite my daughter being fully grown as her knees still give her pain.

The psychological impact cannot be underestimated either. My daughter is of very short stature with both legs being deformed in slightly different ways. She is very aware of being different to her peers and worries about the long term impact her physical appearance might have on her ability to find happiness in a long term relationship. She suffers from low self-esteem and feelings of anxiety about her body. Her difficulty with exercise together with her feelings of low self esteem also make her more prone to weight issues.

As a result of the condition my daughter has also had numerous problems with her teeth: she has had two spontaneous abscesses which have resulted in two rounds of root canal work. This has meant yet more days off school for trips to London for specialist dental treatment at St Thomas's Hospital on a number of occasions. The likelihood is that there will be more in the future. She is also very anxious as there have been lots of issues with the damaged teeth (fillings not lasting more than a day or two on the back of the teeth that have had root canal) which has been distressing for her as she worries about the aesthetic consequences of having such fragile teeth.

The standard medication of phosphate is very cumbersome - the taste is very unpleasant and it is very impractical to have to constantly remember to dissolve and take the phosphate four times each day. At school my daughter is very embarrassed

about it as she doesn't want to draw attention on herself so she only takes the medication before and after her school day, thereby compromising its effectiveness. Obviously when we are on holiday it is also a real burden - on flights, in foreign countries, on days out with friends etc it is a very cumbersome medicine to take. My daughter and I have it constantly hanging over us - how many times has she taken her medication each day.

My daughter is also very aware that there is a high probability that she will pass the condition to any children she has and has already expressed her concern that they would have to firstly face having the pain that she endured, secondly having to take the medication which is unpalatable and impractical whilst not being particularly effective and thirdly having to attend the number of hospital and doctor appointments that have been such a big and negative part of her childhood.

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

I am disappointed to hear that NICE is considering rejecting burosumab (cravings) as a treatment for XLH in the u.k .

I have numerous family members with XLH including my daughter, husband, mother -in -law, nephew, cousins and second cousins.

All are affected in different ways by this debilitating disease including loss of mobility, numerous surgeries, high levels of pain killing drugs including morphine to reduce pain to a bearable level and most have to walk with a stick or use a wheelchair.

A cousin even took the drastic step of a vasectomy as he didn't wish to pass on this awful disease to his children. Had this treatment been available it might have been a different decision.

I have had to witness my husband in considerable pain, having to undergo numerous surgeries to correct bowing of the lower legs and calcification in the tendons around the shoulder joint. All this has led to significant time off work, costly surgery and outpatient appointments.

His bone pain is still on going and some days it is a struggle to even get out of bed.

He was badly bullied as a child over his height and body shape and still refuses to wear shorts or go swimming as he feels people will stare.

My daughter (who is 15) had been on the standard treatment of one alpha and phosphate Sandown since she was 6 months old.

She is considerably shorter than her peers and has had some bullying behaviour towards her. Clothes shopping is difficult and again leads to bullying. Imagine being a 15 year old girl still wearing age 9/10 Clothes. This again is something she has been

bullied over and she finds it hard when she was tsunamis to wear adult clothes like her peers but she is just too small for them.

The conventional treatment has damaged her kidneys and she has stage 2 nephrocalcinosis in both kidneys. This is obviously a major concern that her kidneys could deteriorate in the future.

Day to day she has some bone pain and requires some painkillers several times a week. Running and vigorous exercise is painful.

The 5 times a day routine of medication is extremely limiting and again makes her a target for standing out amongst her peers and she is self conscious and embarrassed that it makes her ' different'.

I really feel that NICE should reconsider its decision as this is the first real treatment for this awful disease that had been developed and it would be a shame if Britain and the NHS , which has been at the forefront of so many medical breakthroughs should fail to give our children the chance at a normal childhood , equal amongst their peers and pain free

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	[redacted]
Conflict	No
Notes	
Comments on the ECD:	
My son has XLH and had been on the standard care of phosphate and calictriol. He had to take 18 pills a day at different times, meaning he had to interrupt his school day to go to the nurse to take medicine. He is short in statue and cannot run as well as his classmates. At night he would often get leg pain. He got upset stomachs from the phospate as well a few times a month. We were so excited for him to get on Burosumab because of the overwhelming evidence from people on the trials of lack of pain, and of growth. And of adults being off a lot of their pain medicines. With the growing epidemic of people being addicted to pain medications as adults this terrified me. One has to look at the cost of the medicine now, verses what the cost of not having the medicine will be down the road with people not being able to stand or work as long hours because of the disease!	

Name	[redacted]
Role	Patient
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	
I am 31 years old and suffer from XLH, I also have a 2 year old daughter that has XLH, Upon reading the findings in this document it has become clear that there is not	

enough research and evidence to properly ascertain whether or not this new drug is going to be cost effective,

This has been written to outline where I think this drug is far more cost effective than the current treatment for XLH

I myself am walking evidence that the current medication and treatment plan does not come close to treating this condition,

I have spent so many weeks, months even years of my life in lots of different hospitals suffering with many different symptoms, so little has been known about this condition that every visit I would have to first explain to a medical professional what my condition even was, looking back at all of those occasions they can all be attributed to XLH, hearing loss, Arnold Chiari, heel spurs, tooth abscesses to name but a few,

I am lucky enough to be currently on the adult medical drug trial for the same drug, I can say that before I was receiving this drug my health was declining at a rapid rate, now however it seems to be stabilised but not getting better,

However before the trial I would struggle to get out of bed in the morning for the excruciating pain in my legs, feet and back. When I did get up the fatigue I would experience would make me want to get back into bed, I struggle to walk up and down stairs, have a shower, put my socks on in the morning, work long hours ect,

I live with chronic pain and fatigue on a daily basis and I have learnt to manage it and just accept that it will be getting worse and there is nothing I can do about it,

What I am really finding very hard at the moment is coming to terms with the fact that I have passed this all on to my daughter, I cannot cope with the knowledge that she will live the same life as me, it breaks my heart to see her walking around with the same waddle that I have, knowing that she will be bullied at school for looking different, knowing that she will have to undergo several very serious operations to correct the damage done by this condition, knowing that all the damage is being done right now will shape the rest of her life

Currently my daughter's specialist doctors are waiting to hear the outcome of this review before they decide to put her through surgery, so if you still decide to refuse funding for the drug she will have to undergo leg surgery immediately, however they seem confident that the leg bowing will heal naturally if given this new drug,

I also find it very hard to accept that there is currently a potential medication available that could mean she does not have to suffer any of that, to say that a medical condition is not cost effective enough to invest money into is very hard to read,

I would agree that investing money into the drug for adults would not prove cost effective as my current condition still means that I live everyday in pain and fatigue but its not getting any worse because of the drug, my physical state will never get any better because of the drug,

But we currently have the opportunity to prevent all children with XLH go through the horrendous procedures that will come with prolonged XLH, the root canal treatments, the leg straightening surgeries, advancing osteoporosis, osteoarthritis, chronic pain to name a few,

I once got told by my specialist that all of her XLH patients are very stoic, I took this as a compliment but upon reflection I feel that the reason we are so resilient in life is because ultimately we know that there is nothing that can be done to make our situation any better,

I beg you to please consider that this is my daughters and my other XLH patients chance of a much happier future, a chance for her not to live a whole life of pain and also my opportunity not to have to live with so much guilt for inflicting this terrible condition upon her.

Many thanks for taking the time to read my comments, if nothing else I feel like someone is listening to us and hearing our experiences with XLH first hand, I do hope that you will fund this new drug for future generations of XLH children,

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

I am a 67 year old who has XLH which I also passed onto my son who is now 40. My own XLH was diagnosed when I was 12 years old and my son's was diagnosed at 15 months of age.

The treatment I received was ergocalciferol or colecaciferol at strengths that would kill a normal human being, so I was told and I also crunched 9 calcium tablets a day. Whenever I could I would throw away the medicines as the calciferol was a thick oil to swallow and the tablets were just chalk and dry. I was dropped from paediatrics at the ripe old age of 14 and transferred to an endocrinologist who arranged my first osteotomy and another at 36. So in all, I had treatment for five years from 14 to 17. I was very short, in pain most of the time which nobody had any patience with even when I was two grizzling that my legs ached walking all the way to town for shopping which was a 2 mile walk with my mum. She was told I had flat feet and my legs would improve their appearance one day and there was nothing wrong with me.

By 12 I was a pretty hardened soul and I did have to face a lot of name-calling and imitation of my walk. They haunt me to this day. I next had a spell of calcitriol and phosphate when I was 36 for 6 months but I developed very high blood pressure. At this time I had a very good job as a computer manager at IBM but my ability to keep up energy dissipated so I had to leave after 12 years and took on a much lesser job. I received no more treatment until 2 years ago at 64 yo. Within 6 months of being on the medicines I was again ill and got hypercalcemia and hypercalciuria whereby I was constantly vomiting, had uncontrollable diarrhoea for weeks and profuse sweating for months. Before my treatment I had hyerparathyroidism which caused forgetfulness, depression and confusion. I had further bowing of legs and arms, severe bone pain and injuries from falling over. I am now back on a lower dose of the calcitriol/phosphate meds with a view to increasing if needed as I am due to have 4 or 5 joint replacements starting off with my knee. I cannot walk without a walker or crutches now and am in a depressed state. My son grew to a better height as he had the benefit of newer drugs which he has been on for the last 38.5 years. Even so, he

is very disabled, cannot work as his back all but supports him now so he lives on benefits.

I would not wish any of my or my son's experience as an XLHer on any of the young 21st century generation. Burosmab is the solution that any of us would have been so happy to receive with its proven improvement of growth in children, bone sturdiness and straight limbs. Even adults in trials have benefited with stress fractures healing (I have at least four stress fractures), and more energy which must surely help them to contribute to society. I wish I could. I am shut in at home, hardly go out and long to be active again.

Please give Burosmab more consideration. The savings in surgery, time off work and school; mental health improvements and others I am sure I haven't thought of cannot be ignored and a long-term view is really required. Contributing to the working world in an average uninterrupted work/career life which is of benefit to the sufferer with better quality of life, to the NHS with far less to outlay, especially in repair surgery and to working life that would eliminate people being registered disabled and a cost to the government rather than a net contributor. I hope you will re-consider how marvellous the benefits of Burosomab to the XLH community and society will be as a whole.

Name	[redacted]
Role	Carer
Other role	Carer
Organisation	
Location	Wales
Conflict	No
Notes	

Comments on the ECD:

I have a 4 year old daughter who has XLH. She suffers with it very badly and has bowed legs. Her pain is getting worse and you can already see that she is of a much shorter stature than children her age. She is currently taking phosphate Sandoz and Alfacialcidol which is a struggle to get her to take 4 times a day. She's always asking why she needs to take all off that medication and why her friends don't.

She does meet the criteria for Burosumab but couldn't get onto the trails as there wasn't enough evidence at the time to say if the phosphate was working or not. Since then it has been proven not to have worked to a good enough standard at all. Having a child with so much pain and knowing that the only drug she can get right now isn't working is heart breaking. I really do hope that you reconsider your options for funding burosumab as it is the only thing that I believe can change her life forever. I am currently pregnant with another girl who through genetic testing has been confirmed that she will have the condition also. As a mother to have one disabled child who might not be able to get this amazing drug to change her life, I know face the unknown with my second daughter to. I break my heart everyday watching my daughter struggle with everyday life and knowing that this drug may be able to change it but might not be funded is devastating.

I just ask you to please please reconsider your options as this is children's lives we are talking about and how they will grow and be as adults. They shouldn't have to be dragged though endless amounts of medicine and surgeries.

Name	[redacted]
Role	Carer

Other role	Parent of adults
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

I'm afraid that the challenge of rare disorders (especially those with a high morbidity, low mortality ratio) is that they are always going to be subject to a cost-effectiveness scrutiny of the potential benefits that so-called Orphan Drugs could bring so that over and over again the result will be on balance it's not worth it to commission the new treatments.

NICE has applied great thoroughness to analysis of this issue; one caveat: there is not necessarily a gender difference in severity of symptoms; individual females may have a different lyonisation potential and so may exhibit markedly less symptoms, but females can be and often are as severely affected as hemizygous males.

I am the father of 2 children with XLH, who received the defective PHEX gene from their mother. Our (female and male) children were each diagnosed at 6 months and maintained at GOSH on 1,25 Vitamin D and phosphate. In both cases radiologic and biochemical parameters of XLH improved under this treatment, but severe bowing of their legs eventuated at the onset of adolescence, resulting in 4 orthopaedic surgeries between them. Subsequently, in her mid-30s, our daughter had femoral and hip surgery further to correct deficiencies in stature and gait. These surgeries did have a profound effect on all of us, as a family, and morbidity continues to stalk us all.

Name	[redacted]
Role	Patient
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

All 4 adults in my family suffer greatly now in adult life due to the deformities and surgery during childhood. Stopping the deformaties developed during childhood would have a huge benefit to health and quality of life during adult life. All 6 members of my family with XLH suffered significant leg bowing to require surgery despite taking current treatment phosphate and alpha since a very young age. It has never stopped the bowing. Quality of life in later years is very low mainly due to the deformities developed. These are also the cause of chronic pain for my family members including my children. We have never had any developments in treatment for this condition. Please allow our children access to this far better treatment. The current treatment is not effective and has awful side effects causing further medical issues such as diahorea and stomach pains.

This condition affects my whole life and most of my family. Please reconsider this decision and this is my only hope of my children not going through even more pain and ending up disabled when there is a better way.

Name	[redacted]
Role	Patient
Other role	Not able to work due to disability

Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	
I suffered severe bowing during childhood despite taking phosphate and alphacalcidol. My teenage son is about to have his 5th operation due to further bowing and he has been on the current treatment since almost birth. It has not worked for either of us or any of the other 5 members of my family who have XLH. I am devastated to hear this news as my son has about 2 years left of growth left and this new treatment has given us hope.	

Name	[redacted]
Role	[redacted]
Other role	
Organisation	[redacted]
Location	England
Conflict	No
Notes	
Comments on the ECD:	

Evidence:

The recommendation appears based on a) uncertainty that the long-term progressive bone disease and ongoing metabolic symptoms of XLH would not be affected by burosumab and b) ICER.

a) The impact of established skeletal damage on long-term outcomes seems to have been underestimated. The long-term adult complications of XLH can be related to ongoing osteomalacia or from consequences of childhood rickets. Any new boney deformity in adults with straight limbs at puberty is at worst mild, as the limbs are no longer growing in adulthood.

Current therapy in childhood with activated vitamin D and phosphate does not treat the underlying disease and does not adequately treat the underlying skeletal and non-skeletal features, leading to short height and bent legs.

The significant adult consequences of short height and bent legs from childhood rickets are:

1. Increased risk of fractures as the bent leg acts as a stress riser. These can either be sub-acute chronic painful insufficiency fractures that then accelerate the underlying deformity or complete fractures requiring emergency hospital attendance.

2. Secondary osteoarthritis with joint pain, stiffness and progressive deformity of the hip(s) and knee(s).

3. Restriction of the range of movement limiting activities of daily living and self-care.

4. Increased fatigue from the inefficiency of mobility that is exacerbated by concurrent muscle weakness.

5. Increased falls risk.

6. Needs for mobility aids.

7. Reduced mental wellbeing from reduced social interaction, employment and companionship.

It is expected that children with well-treated rickets and aligned lower limbs at the end of growth, retain this benefit throughout adulthood. These adults avoid significant adult morbidity and illustrate the long-term benefits from childhood therapy of burosumab.

At £2992 (excluding VAT) per 10 mg vial, the annual cost for a fortnightly maximum dose of 90mg is £700,128 per patient. This is high.

The assumption that as some people continue to have conventional therapy in adulthood (despite its side effects) implies that the disease had not stabilised is in part inaccurate. The use of conventional therapy is adults in controversial increases risk of renal stones, worsening enthesopathy, and tertiary hyperparathyroidism requiring parathyroidectomy. The major indication for conventional therapy in adults is an insufficiency fracture that is often related to bent legs from childhood rickets. The effect of conventional therapy on bone pain in adults is variable and unproven.

Do RSS and RGI-C capture important aspects of XLH?

Do the health states (based on RSS) appropriately map the course of XLH?

By definition the RSS and RGI-C do not capture the long term complications from bent legs as well as the extra skeletal manifestations

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

My wife and son have XLH so I have put myself as carer in the description above as that seemed the most appropriate option in the list

Dear NICE,

In addition to my letter submitted previously, I wanted to make another comment:

There is great need for a new treatment beyond phosphate for the 250 children in the UK with XLH. Burosumab has shown positive results in trial and in my son personally. There are relatively few children with XLH in the UK, which will limit the cost implications. Burosumab has the potential to make such a big difference for those kids, so I think spending money on this new treatment is justified and will be limited by the small number of patients that will require it.

Thanks for taking the time to read this.

Many thanks,

[redacted]

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	[redacted]
Location	England
Conflict	No
Notes	

Comments on the ECD:

The recommendation appears based on a) uncertainty that the long-term progressive bone disease and ongoing metabolic symptoms of XLH would not be affected by burosumab and b) ICER.

The impact of established skeletal damage, sustained in childhood, on long-term outcomes seems to have been underestimated by NICE. The long-term adult complications of XLH can be related to ongoing osteomalacia or from consequences of inadequately treated childhood rickets. Current therapy in childhood with active vitamin D and phosphate does not treat the underlying disease and does not adequately treat the underlying skeletal and non-skeletal features, leading to short height and bent legs, which threatens the health of weight bearing joints (hips, knees, ankles) leading to increased need for joint arthroplasty and other corrective operations in adulthood.

Specifically, the significant adult consequences of short height and bent legs from childhood rickets are:

1. Increased risk of fractures as the bent leg acts as a stress riser. These can either be sub-acute chronic painful insufficiency fractures that then accelerate the underlying deformity or complete fractures requiring emergency hospital attendance.

2. Secondary osteoarthritis with joint pain, stiffness and progressive deformity of the hip(s) and knee(s) and need for repeated orthopaedic surgery.

3. Restriction of the range of movement limiting activities of daily living and self-care.

4. Increased fatigue from the inefficiency of mobility that is exacerbated by concurrent muscle weakness.

5. Increased falls risk and therefore fracture risk.

6. Needs for mobility aids and repeated musculoskeletal therapist input.

7. Reduced mental wellbeing from reduced social interaction, employment and companionship.

8. Markedly reduced potential for securing and retaining paid employment long-term

It is expected that children with well-treated rickets and aligned lower limbs at the end of growth, retain the benefit of such usual growth, throughout adulthood. Accordingly, then adequately treated adults would avoid significant adult morbidity and illustrate the long-term benefits from childhood therapy of burosumab.

At £2992 (excluding VAT) per 10mg vial, the annual cost for a fortnightly maximum dose of 90mg is £700,128 per patient. This is high.

Additional Rheumatological perspective:

I would also add about lower limb deformity increasing problems at ankle. This can cause significant pain and disability which may require surgery. This would be prevented with effective treatment in childhood. Agree there appear significant complications to XLH in adulthood. (Adult) Patient I saw recently had had fracture around pre-existing rod and coincidentally found to have "atypical fractures related to bisphosphonates" (which he had never had and changes really Looser's). He required considerable orthopaedic input and has required to take significant time out of employment. He is in pain, off work and depressed.
Additional Rheumatological perspective:

I would also add about lower limb deformity increasing problems at ankle. This can cause significant pain and disability which may require surgery. This would be prevented with effective treatment in childhood. Agree there appear significant complications to XLH in adulthood. (Adult) Patient I saw recently had had fracture around pre-existing rod and coincidentally found to have "atypical fractures related to bisphosphonates" (which he had never had and changes really Looser's). He required considerable orthopaedic input and has required to take significant time out of employment. He is in pain, off work and depressed.

Additional Endocrine perspective:

Some of my oldest patients have really very debilitating joint pain and stiffness and take fairly heavy duty analgesia to get by with limited mobility. Some have run into problems with renal dysfunction due to excessive NSAID use for instance. Quality of life is significantly impaired due to mobilisation and pain-related problems. Impact on work is also sometimes significant. In those patients where we struggle and have to use phosphate and activated vitamin D later in life, tolerance to high-dose

phosphate can also be very problematic, which adds to poor quality of life, et cetera.

Insufficiency fractures can be very problematic to manage and I've seen these across all age ranges. To counter this, in recent times I have seen some very good results from carefully managed XLH through childhood and transition. In other words, there is still quite significant variability of functional outcome through the early years with XLH.

Additional Radiological perspective:

What has been said for the clinical symptoms/signs also applies to the radiology; persistent and osteomalacia, bowing deformity, stress fractures, fractures, secondary osteoarthritis. Another significant symptom is back pain.

The assumption that as some people continue to have conventional therapy in adulthood (despite its side effects) implies that the disease has not stabilised is in part inaccurate.

The use of conventional therapy is adults in controversial, increases risk of renal stones, worsens enthesopathy and adds to the risk of tertiary hyperparathyroidism evolving requiring parathyroidectomy. Thus adult physicians tend to aim to â€˜run patients undertreated so to avoid such long-term complications. Therapy is often needed at times of skeletal crises however surgery, fracture, bone pain at points of

weight-bearing stress etc. Such problems of course arise in adulthood because of inadequately treated childhood disease. Specifically the major indication for conventional therapy in adults is an insufficiency fracture related to bent legs from poorly treated (with conventional therapy) childhood rickets.

Name	[redacted]
Role	Public
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	
My niece has XLH and needs to take medication 6 times a day. This impacts her life in many ways and requires planning and organisation. It intrudes on her daily life and prevents her from taking part in some activities. As a teenager it is important that she is able to become independent and try out new challenges and experiences without been hindered by the need for regular medication.	

Name	[redacted]
Role	Carer
Other role	[redacted]
Organisation	
Location	England
Conflict	No
Notes	
Comments on the ECD:	

Our daughter [redacted] Allender suffers from XLH and is currently on the burosumab trial.

[redacted] was born with rickets and suffered from bowed legs, soft teeth and is short in stature. She is very brave but we can tell she psychology suffers from these symptoms.

[redacted] is 11, although she fits 7-8 clothes. Her 8 year old brother Tom is now taller than her which is difficult to take. [redacted] also moves from primary school to senior school this summer and is very conscious about her height, to the point she is worried they won't have a school uniform small enough for her.

She had had to undergo surgery on her legs to help straighten them out. This is through having pins inserted above each kneecap which was a painful experience and they are still very sensitive if she knocks them at all.

She has caps on her teeth to help prolong the life of her baby teeth. These are visible and people think that she has bad teeth because she hasn't cleaned them and this clearly isn't the case, which is tough for her to explain.

In addition she is constantly tired and in pain around her joints, especially her legs. So she finds it a real challenge to join in sports or games.

If there was a medicine that could potentially help solve this for [redacted] or any young person, it should be considered for the long term and the burosumab trial so far, has

changed [redacted]'s life.

[redacted] had been taking the standard treatment of supplementing phosphate intake. This entailed taking the medicine 5 times a day and the taste was disgusting. The burden on trying to get a child to take medicine 5 times a day (7am, 11am, 3:30, 8pm and midnight) is significant along with the all the planning needed to ensure we had the medicine with us on the day. We were also lucky to have a great local school that helped, but I am sure this wouldn't always be the case for other children.

The treatment had side effects of severe diarrhoea, terrible wind and severe abdominal pain. The diarrhoea and wind was also a social negative, causing [redacted] acute embarrassment at school on a number of occasions and this impacted [redacted]'s confidence in going out or going on play dates.

Since going on the trial all those symptoms have gone away and [redacted] is more confident in social interactions.

The burden on us as parents is greatly reduced to the point that we didn't realise how much of a burden it was previously until we didn't have to do it under the burosumab trail. Staying up until midnight, then having to wake [redacted] up and then try and get her to go back to sleep after taking a disgusting tasting medicine was not easy on any of us.

Although that burden is lifted, we are totally committed to making sure [redacted] gets the benefit of the burosumab medicine. To that end we are flying back from summer holiday for a single day to get the injection, we have seen that much of a benefit in the new drug.

Since [redacted] has been on burosumab trial we have seen significant changes and benefits.

She has more energy and none of the side effects from the phosphate medicine, such as diarrhoea, bad wind and stomach cramps. This makes a big difference to an 11 year old.

[redacted] has grown since the trial started and because [redacted] feels the new medicine is working she is embracing the process. She is growing and feels better about herself.

This is all down to the burosumab drug, how it is consumed and the reduction in side effects that have greatly improved [redacted]'s quality of life.

We, as parents, feel this will deliver long term benefits to [redacted] and we would ask the consultation board to consider an extended trial at the very least, to really understand the empiric benefits of burosumab that we have observed in a very short trial to date.

As stated already, the trail so far has changed [redacted]'s life.

If successful long term then a negotiation to find a commercial solution must surely be found to deliver such life changing benefits to any child suffering from XLH.

Name	[redacted]
Role	patient and Carer

Other role	
Organisation	
Location	Other
Conflict	No
Notes	

Comments on the ECD:

As someone who has dealt with the disease all my life as I have a real front row view and personal experience in the understanding of how this condition truly effects once life. In my family, we have multiple members with XLH, my Nan (Father Mother now deceased), Aunt and Uncle (Father siblings), My father, Older Cousins (Children of my Aunt/Fathers sister), myself. Younger consign (child of older cousin) and my own son. Every single one of use has be affected on multiple leaves.

Growing up and witnessing the changes that happened my family members only deepened my fear of what my future would hold and how I would have to make tough and difficult decisions about what I truly wanted in life. I still remember the graphic and horrific stories/memories my dad has of the experiments and treatments they would do on him and his siblings trying to figure out ways to right a wrong. Things that include constantly breaking their limbs to straighten them and blood tests and different surgeries all of which has resulted in them all more suffering, pain, and less mobility from which they once were. I saw my father being forced to stop work due to his disability because he was considered to much of a liability for them to have working.

Growing up I would constantly take the phosphate ever four hours and calcitriol twice a day and told it was to strengthen my bones and help me grow. And take it I did, even when it would make me go to the bathroom more then I would comfortably like and make me feel sick in the tummy. I took it until during my adolescence and many years of watching my father and other family members continually deteriorate I said No More I couldn't see the point in putting myself through discomfort if I was only going to end up the say way.

By my late teens I was suffering nerve pinches that would come along without any warning and mostly during school time and literally cripple me. As if high school wasn't hard enough, but now I have the fun of needing to be physically carried to sick bay constantly and I would always struggle with any type of sport as it hurt way too much. I could never participate in ant team sports e.g. swimming, fun runs, cross country, soccer. As I could never keep up and when I did try to play I would be in so much pain and agony that night and next day it just put me off never wanting to do anything. This was always embarrassing, and I hated it, I started to hate myself.

Once I finished school I was needing strong, S8 pain meditation just to get through a work day, within 2 years I went from someone who could work a 12-hr shift on my feet. To struggling to work a 5hr shift even with the medication. I went from someone who was happy and could see so many opportunities in my future to someone who feared waking up everyday not know how much pain I would be in and whether I would be still able to walk or work.

At the age of 20, I knew I would have to make the decision about whether I wanted to have child and risk them getting this condition. Being a mum was something I wanted so badly, I knew it would be a risk as it would mean putting on weight and sacrificing any chance of being able to travel or get a great job as it would take a major impact on my body.

So, at age 22 I fell pregnant and it was a very hard and straining one, I got extremely high blood pressure as even though my baby was average size, for my body he was large. It forced me to have to stop working at 6 months pregnant. Near the end of my pregnancy I went into premature labour at 35 weeks because my body was to small for my baby and I almost lost my son.

But luckily, he come into the work ok, even if it was an emergency C-section resulting it being cut hip from hip, requiring forceps and 22 stables. We had him tested for XLH and it come back negative, and went about life, we tested again a 6 and 12 months old and still now sign of him having the conditions. It was until he was 2 that we notice he was struggling to run and walk, and his forehead was larger, and we knew even before the results came back he had XLH.

My son is a bright happy and cheerful boy, he is extremely smart for his age, but when it came to anything physical he wanted nothing to do with it. As he couldn't keep up with the other kids and he was constantly embarrassed. He never wanted to do sports and anything outside that required a lot of walking or running as it hurt way too much.

So off to Westmead Children we go 3.5 hrs away, we see the specialist and they put him on the same treatment as myself, phosphate, and calcitriol. And the same routine began again, meds every four hrs 24 hrs a day. Constant X-rays, blood tests, Ultra sounds, and trips to Westmead and back, with very minimal change at all. At the age 3 I had notice a small lump on the top/front half of his skull that I was concerned about. Every appointment at Westmead Children with the specialists I would constantly say "I think something is wrong can you please look at this". And constantly I would get push aside with nothing more then "its fine its just part of the disease".

It was 3 months before his 5th birthday that everything started to hit rock bottom he had only just started Kindergarten, he was constantly getting abscesses in his teeth and was in constant pain. We where told he would need to have 3 teeth removed, so down we went to have then surgically removed. Only to come to recovery and find out he had 12 baby teeth removed all because the disease had softened his teeth so badly that there was nothing to protect them from germs getting in deep they all had abscess in them and look like honey comb on the inside. How do you tell a child who brushed his teeth 3 times a day that his teeth where gone? We bring our kids up with the knowledge that if you don't brush them they will fall out. And now I had a 5-year-old who constantly brushed his teeth having half of his removed. Trying to explain he did nothing wrong and it wasn't his fault wasn't easy.

I will never forget the image of my son laying on the bed disorientated, looking like he had been smashed in the mouth as there was just blood everywhere, crying and begging to have his teeth put back. And he still had to go back to school like this. This all happened in March that year.

By the end of May of the same year my son was showing very upsetting behaviour he would come home and have major and I mean major breakdowns over almost nothing and he was so hard to calm down. During these events I would notice the lump on his skull (the one I was told not to worry about) would be larger and more pronounced.

It was just sheer luck that we where seen by a new Specialist and he listened to me, within a week we are having a CT scan. We do our best to stay positive and calm, but I knew something bad was coming. With in less then 2 weeks my son was being

rushed into emergency surgery to have a major skull reconstruction. Turned out the "so called' lump his head with the disks being pushed up from "pressure" because his skull had stopped growing at age 2. And his brain didn't have enough room, it was so bad it has crushed his right optical nerve behind his eye, that we are trying hard to repair. If they didn't do the surgery, then he would have been blinded within 6 weeks. my son has ridges inside his skull, which is an imprint of his brain because the pressure was so bad for so long. (so much for being nothing).

To top it off we where told that he was at risk of needing surgery on his legs because his ankles where at a 45-degree angle and at risk of snapping.

My son has been on burosumab for just over 12 months now and the difference it has made is like nothing I ever thought would be possible. His legs had gone from being the shape of a Bow (from a bow and Arrow) to practically straight, at the start of the trial he was just hitting size 3 clothing and now he is push past size 6-7 clothing. He can RUN with his friends now and wants to play all sport, he can even walk faster then me which is amazing. He is so much happier he is barely in pain now and he has had vertically no abscesses in his teeth, in fact they have also straightened. My cousin and I call this medicine "Liquid Gold" because it is. The results it is having is something we thought we would never see in our life time.

No more getting up through the night to give me son medication, no longer must he miss class time to go and take it at school. It is one small injection every 2 weeks. And knowing that this is something that can help my sons children to have a better and more fulfilling life is such a wonderful feeling. I know longer go to bed hating myself for giving him this horrible disease.

Me, I'm 30 years old on major pain meds like Morphine and Tramadol and I still struggle to do simple things in life. Like clean the house, walk my son 2 blocks to school, work a small shift. I currently hate who I am and what my body has become. I have become depressed and feel useless and like my life is pointless. I mean what is the point of life if you can't have a life. If anything, increasingly every day I am becoming a burden on my friends and family because of my limitation and pain. I struggle to step down even small steps, when I stand up I must wait a few minutes before my legs with let me walk. I can't play with my son outside cause is hurts to much, I cant sit on the floor with him and play, I cant run and jump with him.

And knowing there is a medication out there that could help ease all the pain and give me back even the slightest bit of life and independents is what helps me get through most days. Hoping to wake up and find out that it has been approve and that I might finally get to live again.

Name	[redacted]
Role	[redacted]
Other role	
Organisation	[redacted]
Location	
Conflict	No
Notes	
Comments on the ECD:	
"X-linked hypophosphatemia (XLH), caused by inactivating mutations in the phosphate-regulating endopeptidase homolog, X-linked (PHEX) gene, is the most prevalent form of genetic hypophosphatemic rickets. In children, hypophosphatemic rickets (HR) may present with delayed walking, waddling gait, leg bowing, enlarged	

cartilages, bone pain, craniosynostosis, spontaneous dental abscesses, and growth failure, resulting in short stature. Symptoms in adults with XLH encompass chronic musculoskeletal pain and stiffness, short stature, lower limb deformities, fractures and pseudofractures due to osteomalacia, accelerated osteoarthritis, spinal stenosis, dental abscesses, enthesopathy, hearing loss and fatigue. (Linglart et al 2014)
A combination of active vitamin D and phosphate salts is the current medical therapy used to treat patients with XLH. However, this therapy has certain efficacy- and safety-associated limitations and with current medical therapy the manifestations in children can be improved, but not entirely rescued (Carpenter et al 2011).
In children with XLH, treatment with burosumab, a monoclonal antibody against FGF-23 improved renal tubular phosphate reabsorption, serum phosphorus levels, linear growth, and physical function and reduced pain and the severity of rickets (Carpenter et al 2018). The drug was superior to oral phosphate and active vitamin D in improving rickets in children with XLH after 40 weeks of treatment (unpublished data)
Because studies with burosumab in children have only recently been performed there are no studies investigating whether treatment in childhood with burosumab until end of growth will impact morbidity and quality of life when these children become adults.
Orthopaedic involvement requiring surgical intervention (osteotomy) is frequent in adult patients with XLH and also joint replacement and decompressive laminectomy were observed in those older than 40 years (Chesher et al 2018).
As a scientific organization involved in research of disorders of calcium and bone metabolism, the European Society of Calcified Tissue (ECTS) would like to provide considerations on the clinical and functional outcomes that would affect quality of life in adult XLH patients that have been treated in childhood with burosumab.
Despite the lack of current data, members of ECTS board and Policies & Consensus Committee feel that it is reasonable to assume that if rickets will be treated in childhood until growth has stopped, resulting in the fact that patients start their adulthood with straight legs that are well mineralized, this may lead to a reduction of surgeries for leg deformities and joint replacements for osteoarthritis and improve quality of life later in adulthood. As physicians treating adult patients with XLH we notice the pains and
complications and reduced quality of life related to the bowing of legs, osteoarthritis, (pseudo)fractures and enthesopathy amongst others.
We feel that this needs to be taken into consideration in the evaluation process for reimbursement for burosumab in children.
On behalf of the ECTS
[redacted], Erasmus MC Rotterdam, The Netherlands
[redacted], Dresden Medical Center, Germany

References
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Linglart et al.Therapeutic management of hypophosphatemic rickets from infancy to adulthood. Endocr Connect. 2014 Mar 14;3(1):R13-30. doi: 10.1530/EC-13-0103. Print 2014.
Chesher et al. Outcome of adult patients with X-linked hypophosphatemia caused by PHEX gene mutations. J Inherit Metab Dis. 2018 Feb 19. doi: 10.1007/s10545-018-0147-6. [Epub ahead of print] PMID: 29460029"

Name	[redacted]
Role	Patient

Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	
Comments on the ECD:	
I am 38 years old and very severely disabled. If I had been treated with burosumab as a child I would not be disabled at all. My overwhelming feeling as I first read of this treatment was sheer joy in the fact that no one would ever need to get this bad with this condition ever again. I live every day in agony. I rely on carers, ceiling hoists, wheelchairs and other specialist equipment. I survive on a cocktail of medications and attend dozens of appointments- all of it in severe pain. This could be prevented in others. The way the kidney wastes phosphate instead of absorbing it can be successfully treated with this new drug (Burosumab) so to deny it to people would be to roll the dice on whether you were making them face a future being severely disabled, a little bit disabled or able bodied but with pain. The sheer amount of NHS treatment I have had over my 38 years far outweighs anything it would ever cost to provide Burosumab over a lifetime and prevent all the broken bones, respiratory defects, muscle weakness, kidney stones, pain medication, phosphate and calcitriol treatments, repeated blood tests, repeated xrays, plaster casts, a&e hours and all the other drugs and appointments spent treating the side effects of oral phosphate. It might seem like an expensive drug but if you look at what can happen without it, you'd be saving the NHS a lot of money by approving it.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	USA
Conflict	No
Notes	
Comments on the ECD:	
I live in America and have an 8 year old daughter with XLH. She had been on standard treatment for 7 years and was still not able to achieve a phosphorus level even close to normal. She had horrible side effects: intestinal issues, headaches, and renal calcination. She still had substantial bowing of her legs and required 2 surgeries to help. She has been on Crysvita for 1 month and immediately her phosphorus level is perfect. All of her intestinal issues are gone, and she has already grown from straightening. This drug is a cure and essential for patients with XLH.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	England

Conflict	No
Notes	
Comments on the ECD:	
My name is [redacted] I'm 24 years old and suffer with XLH. Growing up with XLH has been extremely difficult and affects every aspect if my life. Growing up as a child with XLH i was always in a lot of pain, particularly in my legs and feet. The only treatment for XLH growing up was taking potassium phosphate and calcitriol everyday. The Kphos tasted absolutely disgusting and my mother had to always make sure we took it even though i would try and avoid it my best because as a child i didn't understand how important it was. Since I've become an adult my symptoms from the XLH have gotten worse from 18-24 than they ever did growing up as a child. I have had sever spontaneous dental abcesses forming, one resulting in losing my front tooth. I have lost signifigant hearing in my left ear and now suffer from unbearable tinnitus. XLH has caused hyperparathyroidism in me which causes me to be hypercalcemic. The excess calcium in the blood means the kidneys have to work harder to filter it and this causes calcium to build up and kidney stones form. I have had to pass several kidney stones and it is excruciating. Hypercalcemia also leads to me feeling nauseas and light headed. The excess calcium is taken from the bones when parathyroid hormone is released making them weaker causing bone and muscle pain and weakness making me feel tired and fatigued a lot. Excess calcium in the blood affects the brain which affects my concerntation, causes lethargy and depression. If the Burosumab was available then i wouldn't have to suffer as much with all these side effects and if it was available when i was growing up then i wouldn't have had such a traumatic upbringing and would have been able to fit in going to school and would have been able to achieve a lot more. Even since I turned 16 i have basically been left untreated as there isn't any treatment for adults apart from surgery for when it gets really bad. Everyone with XLH should be able to get the new burosumab treatment as XLH doesn't just stop affecting you after you stop growing. It is a degenerative condition and will not get any better, especially if theres no treatment available. When i was growing up it was mostly my legs that hurt and now I'm in constant pain all over and need treatment. Burosumap is available to patients with XLH in the united stated and is working for everyone i have talked to or heard from in the XLH community over there. Please reconsider approving this medication for children and adults with XLH in the uk, we need it as it is the only promising treatment to help us.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	United States
Conflict	
Notes	
Comments on the ECD:	
Phase 3 participant in burosomab trial in united states. I would like to voice support for using burosumab. I have XLH and have been a participant in phase 3 trial for two years and have seen significant improvement in quality of life increased mobility and	

reduced pain. On a subjective side I feel preventing long bone deformity and pain in children will reduce surgical exposure for a person and less exposure to opioids. Decreasing lifelong pain and exposure to opioids will undoubtedly benefit an individual reducing risk to addiction. Further avoiding longbone deformity from childhood will make for increased mobility and exercise capability which will further drive down the risk for sedentary related illnesses that have humongous long term cost associated with treatment like diabetes and heart disease. Thank you very much

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	No
Notes	

Comments on the ECD:

I write as a close family friend of an affected young person. I am also a paediatrician and I see this young person's illness in the context of my experience of managing children with chronic health conditions. I am not an endocrinologist and cannot comment on the medical efficacy of the treatment. This is not a medication which I would prescribe.

The young person I know was diagnosed with XLH around the age of 3 and is now 15. Over this time I have had close contact with the family (at least weekly, including many shared holidays). She takes 8 lots of medication every day. This means an 8x daily reminder that she has a chronic health condition and that she is different from other children. This act in itself reinforces the stigma in her own mind. In addition to this, the responsibility falls on the adults around her to ensure that her medication is available and to remind her take it. We know that childhood and adolescence is a critical period for physical, intellectual and emotional development, but also for developing a key sense of self - who am I? where do I fit into the world? do I have freedom and agency as a young person? I have witnessed the direct impact that this relentless reinforcement has had on this young person in comparison to her peers and siblings. I believe that there is a huge benefit in psychological wellbeing for a person having a single injection of medication every 2 weeks compared to several times per day. This in itself will, at a population level, be more likely to promote good mental wellbeing later in life. For children in families where medical compliance is an issue, the use of burosamab will also improve physical outcomes.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	
Notes	

Comments on the ECD:

A close friend has a child who would benefit from this medication. Apart from the potential improvements to quality of life brought about by the effectiveness of the new treatment, the positive impact of being able to reduce the 'dosage' of medication from 4 - 6 times per day to once every two weeks for children would be very significant for example for their educational, social and emotional development.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

I would strongly urge you to reconsider the benefits of this treatment for this very complex and difficult condition.

I am the carer of a child who is diagnosed with XLH. My child has taken part in the study of this drug and I want to make you aware of the improvements I have seen whilst this has been undertaken.

Prior to the study, my child was on the traditional treatment of phosphate and alfacalcidol. This was administered 6 times per day. This was difficult and extremely distressing for my child to take. Phosphate is a very nasty tasting drug. Due to the problems administering it, I was never sure if the full dose had been given. It was extremely difficult to have support at school to have this administered regularly throughout the day and was very disruptive to daily life in general, which makes the treatment less effective and has an impact on managing this very complex condition.

Prior to the trial, my child had been unable to maintain a constant level of phosphate and calcium. The dosage was constantly adjusted but made very little difference. Since taking the burosumab injections, there has been a significant improvement in his levels and he has maintained a relatively constant level in his blood and has had much improved results.

There has been a significant reduction in the bowing of his legs and the gait between the legs has reduced. He has also maintained healthy growth maintaining growth above his growth line. However, prior to the study he was always below and struggled to follow the growth pattern. This has boosted his self esteem as this condition is devastating on growth. I do not think these results would have been present on the traditional treatment at all.

On the traditional phosphate treatment, my child had increased bone/joint pain. Since the trial, he has had significantly reduced pain levels and as a result has had better movement and been able to participate in activities.

The phosphate /alfacalcidol treatment caused significant upset stomachs, sickness, abdominal pain and stomach bleeds. This resulted in several hospital admissions and the symptoms were all diagnosed due to the severity of phosphate dosage. However, there was no option not to take it, so it was just an endless cycle of pain, discomfort and distress. Since the injections of burosumab there have been none of these symptoms present at all.

My child has found the injections very easy to deal with in comparison to the traditional treatment. I am confident that he always gets the full dosage, thus giving the optimal treatment.

Also, my child experienced severe dental problems which had resulted in constant severe painful dental abscesses which had been present since the age of the 3. This has required NHS hospital visits and has resulted in several extractions at the hospital. Since taking the burosumab, there has been a significant improvement in his dental health. The dental abscesses have completely disappeared and there has been a significant improvement in his dental health. The dental hospital have been able to transfer his care back to his own dentist.

In summary, my child has better results, health and wellbeing and at the same time resulting in less visits to hospitals/dental hospitals. If this treatment was to be continued throughout childhood, I am very confident that he would have an improved quality of life with his bone health in general and being able to manage this condition.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

I am an adult with XLH and feel that after 40 years there has been no real breakthrough in the treatment of this devastating and complex condition until now. I have struggled to get consistent treatment as it is a complex and an uncommon condition. I have been on the standard treatment of phosphate and alfacaldicol since childhood.

I have undergone and continue to undergo multiple complex orthopaedic procedures to correct the deformities that this condition caused in childhood and continue to struggle with fractures and extremely weak bones. I have undergone extensive prolonged hospital stays and extensive prolonged rehabilitation programmes. the cost burden on the NHS of this is huge.

I have also had severe dental problems leading to multiple dental operations and have lost teeth through recurrent painful absences, which have been present since childhood.

I would not want my child to experience these difficulties later in life, when there is a chance to better control this condition with this treatment. "

I would strongly urge you to reconsider the benefits of this treatment for this very complex and difficult condition.

Name	[redacted]
Role	Carer
Other role	[redacted]

Organisation	
Location	England
Conflict	No
Notes	

Comments on the ECD:

My middle child [redacted], aged 11, has X-Linked Hypophosphatemia. She was misdiagnosed at 1 as they thought she had Blount's Disease. We eventually after 6 months were diagnosed at The Evelina Children's hospital London. She was given Phosphates and Alphacalcidol to take 5 times a day. She has been taking this combination of medicine for 10 years.

[redacted] grew very slowly and sadly we were not told for 8 years of those that she cannot take dairy 30 minutes before or after taking the phosphates as the phosphates bind with the calcium and are therefore not absorbed and flush straight out of her system. It wasn't until she came under the care of Dr Cheung , moving on from Dr Hulse that she advised us of this. I feel that 8 years of her life were wasted due to ineffective diagnostic prescription . Forgetting about amounts, the side effects from the phosphates have been embarrassing and demoralising for [redacted]. Not only has she had to deal with chronic pain and chronic tiredness she has had to deal with Excessive wind, stomach pain and chronic diarrhea as a side effect of the phosphates. [redacted] was given a card at school which meant she could go to the toilet at any time but if another child was in the bathroom at the same time she said she would tell a lie with her fingers crossed behind her back saying that the smell wasn't her. Touching on the psychological effects of not reaching her full skeletal growing potential, she became very angry when her younger brother over took her in height and became the same shoe size as her. [redacted] was always being asked her age by peers and would receive sniggers when she gave it to them. Hatty has always been on or below the zero percentile for her height. She is lucky though as she has an amazing personalty and a very supportive family to guide her through life.

Talking now from my own personal point of view, being her mum, I have taken full responsibility for administering the phosphates to her over the last 10 years and it is not until now, that she has started on the drug trial with Bursomub, that I can fully appreciate how stressed I have been constantly watching the clock, every 3 hours, of every day, making sure, wherever she was that she has access to her phosphates and have a supply at hand in case the solution was spilt or [redacted] accidentally had some milk without thinking and making sure I could wait another 30 minutes before she had another dose of phosphates made up ready to be administered at that time. [redacted] would cry cry cry taking this medicine, she hated it. She would be angry at her brother and sister that they didn't have to take it. We underwent a course of psychotherapy at The Evelina which worked for a short time to see her through her anger.

Last October [redacted] underwent very painful surgery to insert metal pins and plates either side of her top of the knee growth plate to try and correct her deformed legs. She is still in immense pain with these plates in and especially if they bang together .

Burosomub has changed not only [redacted]'s right to a quality of life but has let her be the child that she deserves to be. [redacted] is free to play with her friends. She has grown more in the last month than she has grown in the previous year. The deformed legs have straightened. I have been able to be her mum, not her nurse. [redacted] has just started puberty and so as the medical world knows, girls continue to grow for up to 2 years after they start puberty. We feel it is vital for [redacted] to continue on Burosomab for as long as possible to make sure that she gets the healthiest skeleton

possible, setting her up for the rest of her life and possibly avoiding any medical interventions in the future.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Europe
Conflict	
Notes	

Comments on the ECD:

This illness is severe problem in adult age, with a lot of pain, stiffness and microfractures in the whole body that result in a low life quality than healthy people. With the treatment that exists we need a lot of surgery and medicines with a lot of unwanted side effects. And it also results in a shorter work carriere with a lot of sick leave .With Crysvita we will be able to live a more normal life. As it is now we always need to carry the medicines with you and something to disolve the medicine in up to 5 times a day in a cooler, this will also create a lot of trouble while travelling, crysvita i s a single injection a month. It is a real pain to have this as a child and always need to take medicines several times a day and also learn teachers and child carers to adminstrate this. Another problem as a child with XLH always will try to avoid the medicines because of a really bad taste, and it is almost impossible to hide in other food or drink. It will be a whole new world with Crysvita as a child but also as an adult. I'm telling this on behalf of myself, my daughter, mother, aunt and cousins that all have XLH and suffer in a lot of ways because of the inferior treatment that is given today. A lot of the suffering as an adult is a result of the treatment as a child, the medicines and a lot of side effects

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	Europe
Conflict	
Notes	

Comments on the ECD:

I am a 37 years old woman from Denmark, and was diagnosed when I was about 18 months. When I was growing up I didn't realise I had XLH other than I had to take medicines and pack many bottles when I went on school trips or visited with family. I was mostly bothered by my lack in height and the fact that I did not have the same energy level as the other children my age. I mostly recall being the last one in the group when running or going for a bike ride and really having to push myself to keep up with the other children. My parents had arranged with my teachers that I was allowed to say when I could not particape in physical activies and the managed not to make me feel different. I was never teased.

When I was about 13 I had a knee surgery - after the surgery I was still able to be physical active for my teenage years and I only felt a few limitations as for example not being able to jump high or on trampoline.

When I was about 19 I had a new knee surgery - and I again didn't connect it XLH mentally - what I mean by that comment is that I didn't realise it would get worse. It was not part of my identity at the time. Looking back with my knowledge today I of course realise that it naturally was part of my XLH.

In the beginning of my twenties I started to feel a lot more limitations - I was during my years at university where I stopped being able to ride a bike and had to be very careful not to push myself with too long walks etc. because it would mean lying down with my kneew up. I was also in those years I started getting more problems and feeling more limitations. I was naturally difficult mentally for me at the time, because I realised that my health would not improve, but at the same time I am quite strong and have developed a strong mechanism of hiding away my worries.

In order not to write too much text, I have listede some of my symptoms/effects of XLH that especially have eveloped during the last 5-10 years and that bother me the most:

- Constant back pains and neck pains (stiffened and limited movement especially when trying to look to the right or left, up or down. Difficult to find a resting point when trying to sleep)

- Ruined elbow joint on one side(affects me alot - only movement about 10 degrees) - specialists does not recommend surgery because of the XLH Osteoarthritis in both knees (quite bothered)

- Limited movement in jaw - am not able to open my mouth more that 2cms (quite bothered)

- Wrist pains - gives limitations to movement

- Osteoarthritis in hips (not to bothered - does affect my ability to bike)

The last few years have been quite hard as my limitations and pains have become worse. Mentally I am quite strong and stubborned and continue to work full time and hope to be able to do so for more years to come.

For me the standard conventional treatment (which I still take) has not proven to be helpful enough - eventhough I feel that my childhood has not been effected alot by the XLH, where I mainly had problem of being annoyed with not being able to keep up physically. As an adult I have been quite "surprised" of the affects and symptoms of XLH that I have now. I am of the strong belief that the conventional treatment is not good enough - it definately has not been for me. My fear is that the long term effects of XLH on the bones are not obviuos for the medical specialist because the are not visual as a child.

Two years ago I was fortunate to give birth to twin girls, where one of the has XLH.

I would never call her medicin treatment and hospitals a burden because she is a gift. Naturally we do have many hospital visits with bloodsamples, checkups, urine samples, physiotherapy, and it can be quite stressful for at family with small kids, especially due to the need to take time out from work and having the approval to do so.

My daugther recieves phosphate 5 times a day at the following times and naturally also receive calcitriol (etalpha) and d-vitamins:

- 06.50 am

- 11.30 am

- 16.20 pm

- 21.10 pm

- 02.00 am

She recieves her phosphate medicines twice while sleeping and luckily she hardly wakes up. Both me and my partner take the medicine times quite seriously and do tend to be a bit devasted if we accindently do not wake up at 2 but an hour to late. That part can be quite stressful, because we want to do the very best for her. I think this is one of the most

stressful thinds. Other than we have come accostumed to bringing medicines with us everywhere and luckily my daugther is quite good at accepting to take her medicin. We have have only problems one time during illness.

My biggest concern is of cource that what we are doing is not good enough - eventhough we do all the things that the treatment requires and extra things such as training with childrens physiotherapy and look for experts. My daugther unfortunaly stills shows signs of XLH on her bowed legs, and sway back. It is hard being told that we are doing all that can be done and the current time and still seing an active XLH in her.

As I wrote earlier I am quite strong, eventhough the last few years have been hard because a worsening of my XLH. I have become quite good at not feeling my pains, so for me the limitations are the most difficult where not beeing able to take care of my girls alone for too long is the worst. I physically need a lot of brakes and it takes alot for me to change diapers etc.

Kind regards,

[redacted]

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Burosumab for treating X-linked hypophosphataemia

ADDENDUM

Table of Contents

This document contains a critique by the Evidence Review Group (ERG) of the new evidence presented by Kyowa Kirin in response to the evaluation consultation document (ECD) produced by NICE.

1. CLINICAL EFFECTIVENESS

1.1 Trial C301

CL301 is a multicentre, randomised, open-label, Phase 3 study comparing the efficacy and safety of burosumab with active control (oral phosphate/active vitamin D therapy) in children with clinical evidence consistent with XLH (aged 1 to ≤12 years). The trial is small with 29 children randomised to burosumab and 32 to conventional therapy.

This was an open label study, blinding was not applied in the study. Although the ERG agrees that blinding would be problematic due to the different methods of administration and the individualised nature and frequent dose adjustments needed with oral phosphate/active vitamin D therapy, this still means that the study is at high risk of bias. However, the primary endpoint was assessed by three independent blinded paediatric radiologists using the RGI-C scale.

Here only results from the primary analysis at Week 40 are presented. This is a very short follow-up period for children who will continue to use the drug until they are 16 or 17 years.

There were some differences in patient characteristics between the two treatment groups: patients in the conventional therapy arm had received prior conventional therapy for [redacted] patients in the burosumab arm; they were [redacted] and had started conventional therapy [redacted]. Baseline height (z-score) was also lower in the burosumab arm. Given the small numbers of patients included in both arms, these differences could have influenced results.

Results from study CL301 are reported in Appendix A of the company's response to ECD.

The primary endpoint showed that burosumab significantly improved rickets compared to conventional therapy. RGI-C Global scores at week 40 were 1.92 (SE=0.110) for burosumab and 0.77 (SE=0.107) for conventional therapy (difference=1.14 (95% CI: 0.83 to 1.45)). For RSS Total score the difference in change to week 40 was -1.34 (95% CI: -1.74 to -0.94), favouring burosumab.

In terms of growth and walking ability burosumab showed no statistically significant improvements when compared to conventional therapy. The Patient-Reported Outcomes Measurement Information System (PROMIS) was developed by the National Institutes of Health and uses domain-specific measures to assess patient well-being. The company states that the minimal important difference (MID) was set at [redacted]. At Week 40, the difference from baseline in the burosumab group was [redacted], and therefore reached the MID. In terms of pain (The Faces Pain Scale – Revised (FPS-R); for children ≥ 5 years of age at the Screening Visit) and quality of life (SF-10 for Children Health Survey; for children ≥ 5 years of age at the Screening Visit)

[redacted].

The key new statistically significant change reported from study CL301 is an improvement in rickets symptoms (based on both RGI-C and RSS scores). No statistically significant changes were observed for [redacted]growth and walking ability, [redacted]. As discussed in the original ERG appraisal, this reliance on rickets scores, which do not fully capture the diverse physiological impacts of hypophosphataemia that may be independent of rickets, is a limitation.

1.2 Comparison with studies CL002, CL201 and CL205 in the original CS

There were differences in inclusion criteria between the different studies (see Table 2 in the appendix below):

- CL002 (conventional therapy): Paediatric patients with XLH, 5 – 14 years old.
- CL201 and CL205 (burosumab): Radiographic evidence of active bone disease including rickets in the wrists and/or knees, AND/OR femoral/tibial bowing, OR, for expansion patients, an RSS score in the knee of at least 1.5 points as determined by central read.
- CL301: Radiographic evidence of rickets with a minimum rickets severity score (RSS) total score of 2 as determined by central read.

As mentioned in the ERG report "study CL002 [conventional therapy] included all children with XLH, while study CL201 [burosuman, aged 5-12 years] included children with more severe symptoms of XLH." As can be seen from the inclusion criteria, study CL301 included children with more severe symptoms of XLH than studies CL002, CL201 and CL205.

The dose of burosumab in study CL301 was different from the dose in studies CL201 and 205 (see Table A1 in the appendix below):

- CL201: Multi-dose burosumab; Biweekly (once every two weeks) or monthly administration of burosumab (doses 0.1 to 2.0 mg/kg).
- CL205: Multi-dose burosumab; Biweekly (once every two weeks) administration of burosumab at a target dose of 0.8 mg/kg.
- CL301: Patients assigned to the burosumab treatment group received burosumab at a starting dose of 0.8 mg/kg every two weeks (Q2W). The dose may be increased to 1.2 mg/kg at any time during the study if a subject meets specific dose-adjustment criteria (see Appendix A, response to ECD).

As can be seen from the Table with patient characteristics from studies CL002, CL201, CL205 and CL301 (see Table A2 in the appendix below), there are considerable differences in patient characteristics between the studies. Most of these are a direct consequence of difference in the age of included children (weight, height). However, the following characteristics are different between studies:

- Study CL301 included more [redacted] children than any of the other studies.
- Mean (SD) standing height z-score was [redacted] at baseline in CL301 than in any of the other studies.
- More children in CL301 had a renal ultrasound score of [redacted].

- Mean (SD) RSS Total Score was [redacted] at baseline in CL301 than in any of the other studies.

Given these differences results from study CL301 are difficult to compare with results from the observational burosumab studies. Nevertheless, results from study CL301 are shown in Table 1 together with results from studies CL201 and CL205.

Table 1: Results from studies CL201, CL205 and CL301 at 40 weeks

	CL301 (1-12y)	CL205 (1-4y)	CL201 (5-12y)
RGI-C Score	1.92	2.33	1.72
% substantial healing	72%	100%	69.2%
RSS Total change at 40 wks	-2.04	NR	-0.89
Source: CS, Table 17, page 94; CS, Table 24, page 109 and Appendix A, Response ECD			

In study CL301 29 children were randomised to burosumab, [redacted] children were 1-4 years old and [redacted] were 5-12 years old (see Table 5, page 9). Therefore, results for study CL301 should be approximately halfway in between the results of studies CL201 and CL205, ignoring the differences in inclusion criteria and patient characteristics.

In Table 5 of Appendix A (page 9) the company presents results from study CL301 by age group. RGI-C Global score for children aged <5 years was [redacted], compared to 2.33 in the same age group in study CL205; and RGI-C Global score for children aged ≥5 years was [redacted], compared to 1.72 in the same age group in study CL201. It is not clear why younger children had a higher RGI-C Score when comparing results from the observational studies (CL205 versus CL201), while in the RCT older children in the burosumab group had a slightly higher RGI-C score compared to younger children. Possible reasons for differences in results are the different inclusion criteria in the studies and differences in the doses of burosumab.

It is also important to highlight the potential effect of baseline RSS on outcome. In study CL201 this effect was explored and burosumab showed better results for children with more severe baseline rickets scores. In the Q2W-treated higher RSS subgroup (baseline RSS total score ≥ 1.5; N = 17), RSS total score was reduced by 71% at week 40 (LS mean [SE] change: -1.68 [0.109], p < 0.0001) and by 62% at week 64 (-1.44 [0.128], p < 0.0001). In the lower RSS subgroup (baseline RSS total score < 1.5; N = 18), treatment with burosumab for 40 and 64 weeks [redacted]. Therefore, it is important to consider this effect in the light of the high baseline RSS in study 301 (see Table 3 of the appendix below), thus implying that any effect in clinical practice might be considerably attenuated if RSS is much lower in clinical practice than in study 301.

1.3 Adverse events

The burosumab safety profile observed in study CL301was generally consistent with that seen in the other burosumab paediatric XLH studies. It was reported that there were no treatment discontinuations and no deaths during follow-up in the study.

Based on other burosumab paediatric XLH studies, the most common adverse drug reaction reported in paediatric patients up to 64 weeks treatment with burosumab was injection site

reactions (57%), headache (54%), pain in extremity (42%), vitamin D decreased (28%), rash (23%), toothache (19%), tooth abscess (14%), myalgia (14%), and dizziness (11%). Approximately 57% of the patients had an injection site reaction. The injection site reactions were generally mild in severity, occurred within one day of medicinal product administration, lasted approximately one to three days, required no treatment, and resolved in almost all instances.

In study CL201, one patient experienced serious TEAEs, and two patients experienced non-serious severe (grade 3) TEAEs; all other TEAEs were mild or moderate (grade 1 or 2). All 52 patients (100%) experienced at least one TEAE during the study. The most frequent TEAEs (>30% incidence) in study CL201 were [redacted].

The most frequent TEAEs (> 30% incidence [four or more of 13 patients]) in study CL205 were [redacted]

In study CL301, [redacted].

The most frequent treatment-emergent adverse events (TEAEs) in the burosumab group (by preferred term, >30% incidence) were [redacted]. In the burosumab arm, 45% of patients had injection site reactions (grouped terms), all but one were mild and none were considered serious.

TEAEs related to treatment (i.e., TEAEs deemed “definitely,” “probably,” or “possibly” related to study drug by the investigator) reported at a greater frequency (≥10% difference) in the burosumab arm compared to the oral phosphate/active vitamin D arm were: [redacted].

2. COST EFFECTIVENESS

2.1 Changes to the company's economic model

The changes made by the company to the previous version of the model are discussed in this section and summarised below:

- Including the results of the Phase 3 study (transition probabilities).
- ERGs preferred method of calculation of transition probabilities.
- Costs of adverse events associated with burosumab (as preferred by the ERG).
- Amendment to age at which treatment is stopped.
- Correction to the calculation of utilities during childhood
- Incorporation of new long-term utilities in adulthood.
- A patient access scheme (PAS) resulting in a [redacted] discount of burosumab original list price.

2.1.1 Transition probabilities

Additional clinical evidence on burosumab from the 40-week Study CL301 was included in the economic model in the form of updated transition probability matrices for both burosumab and standard of care.

Burosumab

The 40-week observation matrix for burosumab from Study CL301 is given in Table 2.

Table 2. Observation matrix for burosumab (Study CL301, baseline to week 40)

	Mild	Moderate	Severe	Healed	Total
Mild	0	0	0	0	0
Moderate	2	1	0	0	3
Severe	16	8	1	0	25
Healed	0	0	0	0	0
Source: Table 1 in company's response to ECD (Appendix B).					

Note that Study CL301 only included XLH patients with an RSS total score larger or equal to 2.0. Therefore, there were no observations of patients in the healed or mild health states at baseline. For that reason, transition probabilities in the new version of the model could not be based on Study CL301 only. Thus, to model transitions between all the health states of the economic model, data from CL301 has been combined with the results from CL201 and CL205. This was done by calculating the expected 1-year observation matrix from CL301, CL201 and CL205 using the method and R code proposed by the ERG in the ERG report. The expected 1-year observation matrix for CL301 is shown in Table 3.

Table 2. Expected 1-year observation matrix for burosumab (Study CL301)

	Mild	Moderate	Severe	Healed	Total
Mild					
Moderate	2.3	0.7	0.0	0.0	3
Severe	18.5	6.0	0.5	0.0	25
Healed					

Source: Table 3 in company's response to ECD (Appendix B).		

The expected 1-year observation matrices for CL201 and CL205 are the same as in the ERG report and can be obtained from the company's electronic model. The three expected 1-year observation matrices were combined together, resulting in Table 4. Based on this, the transition probability matrix used for burosumab is shown in Table 4. Note that unlike in the original analyses, where the company distinguished between patients younger and older than 5 years, the company used now only one transition matrix for all ages in the burosumab arm (i.e. Table 5). This is achieved by choosing the option "Match age 5+" in the new version of the model for burosumab patients younger than 5 years.

Table 3. Expected 1-year observation matrix for burosumab, combined data from Study CL201, CL205 and CL301

	Mild	Moderate	Severe	Healed	Total
Mild	5.6	0.0	0.0	3.4	9
Moderate	7.4	5.9	0.0	0.7	14
Severe	29.4	12.8	0.5	0.3	43
Healed	0.0	0.0	0.0	1.0	1
Source: Table 4 in company's response to ECD (Appendix B).					

Table 4. Transition probability matrix for burosumab, combined data from Study CL201, CL205 and CL301

	Mild	Moderate	Severe	Healed	Total
Mild	61.8%	0%	0%	38.2%	100%
Moderate	53.1%	41.9%	0%	5%	100%
Severe	68.4%	29.7%	1.2%	0.7%	100%
Healed	0%	0%	0%	100%	100%
Source: electronic model in company's response to ECD.					

Standard of care

For the standard of care, the same approach as for burosumab was taken by the company and the data from CL301 were combined with the UK chart review data (assuming last observation carried forward). The 40-week observation matrix for standard of care from Study CL301 is given in Table 6. The expected 1-year observation matrix for the standard of care is shown in Table 7 and the corresponding transition probability matrix is presented in Table 8.

Table 6. Observation matrix for standard of care (Study CL301, baseline to week 40)

	Mild	Moderate	Severe	Healed	Total
Mild	0	0	0	0	0
Moderate	1	5	1	0	7
Severe	3	7	15	0	25
Healed	0	0	0	0	0
Source: Table 6 in company's response to ECD (Appendix B).					

Table 7. Expected 1-year observation matrix for standard of care (UK chart review LOCF and Study CL301)

	Mild	Moderate	Severe	Healed	Total
Mild	31.0	5.0	4.0	4.0	44
Moderate	10.3	39.5	6.3	2.0	58
Severe	8.8	19.7	87.5	4.0	120
Healed	1.0	1.0	2.0	10.0	14
Source: Table 8 in company's response to ECD (Appendix B).					

Table 8. Transition probability matrix for standard of care, combined data from UK chart review (LOCF) with CL301

	Mild	Moderate	Severe	Healed
Mild	70%	11%	9%	9%
Moderate	18%	68%	11%	3%
Severe	7%	16%	73%	3%
Healed	7%	7%	14%	71%
Source: Table 9 in company's response to ECD (Appendix B).				

ERG comment:

In general, the ERG could reproduce the observation and transition probability matrices based on Study CL301 for both burosumab and standard of care. There were minor discrepancies in some of the estimated probabilities but the ERG believes this was due to rounding the number of observations. The transition probability matrix for burosumab (Table 5 above) was incorrectly reported in Appendix B of the company's response to ECD (it referred to Study CL301 only and not to the combination of CL201, CL205 and CL301) and was sourced from the new version of the electronic model.

It should be noted that Study CL301 included patients from ages 1 to 12 years but the model requires two different transition probability matrices for burosumab depending on the age of the patients (one for patients aged 1 to 4 years and one for patients aged 5 years and older). In the previous version of the model (and therefore in the analyses presented in the ERG report) the company distinguished between these two groups of patients by providing two different transition probability matrices (instead of pooling them together). It is unclear why data from Study CL301 were not separated by age to estimate two different transition probability matrices based on the age cut-off. This basically means that, in the previous approach by reporting transition probability matrices separately, the company implicitly assumed a treatment effect that varies with age. However, in the updated analyses based on Study CL301 data, a pooled transition probability matrix was estimated for burosumab. Thus, the company implicitly assumed that there is not a treatment effect depending on age. The approach taken in the updated analyses seems therefore inconsistent with the approach taken in the original analyses. This issue should have been discussed in the submission of the new evidence. A justification for the assumption made should have been provided as well. This justification should be based on clinical expectations and not on data availability or influence on the ICER. Nevertheless, given the model structure and all the analyses conducted in the ERG report, the ERG does not expect

that this assumption, even though it might be methodologically flawed, has a large impact on the ICER.

Table 9 below shows a summary of the approach taken by the company when choosing the transition probability matrices, before and after the Study CL301 data were available and the ERG judgement on this approach. Besides the issue of considering two or one pooled transition matrices for burosumab, there is another potential issue that requires further justification from the company. In Question B24 of the clarification letter the ERG asked the company to explain the meaning of the option called "Match age 5+" for the transition probabilities in the burosumab arm for 1-4 years old patients. The company's response was the following:

> "*This is to explore a scenario in which only transition probabilities from the CL201 study are used. We do not consider this to be a relevant scenario which is why the results were not included in the submission*".

Given the above answer, the ERG cannot understand why this option was chosen by the company in the revised analyses.

Compared to the original analyses, the transition probability matrix for burosumab age 5+ in the revised analyses is inconsistent. This includes CL205 data, which refers to patients aged 1-4. The ERG agrees with the choice of the transition probability matrix for the standard of care in the revised analysis.

Table 9. Transition probability matrices chosen by the company before and after Study CL301.

	Company's original analyses	**Company's revised analyses**	**ERG judgement**
Burosumab Age 1-4	40 week extrapolated to 1 year	Match age 5+	Requires justification
Burosumab Age 5+	64 week extrapolated to 1 year	Combined CL201, CL205, CL301	Requires justification
Standard of care	UK data (LOCF)	CL301 with UK LOCF	Agree

2.1.2 Adverse events costs

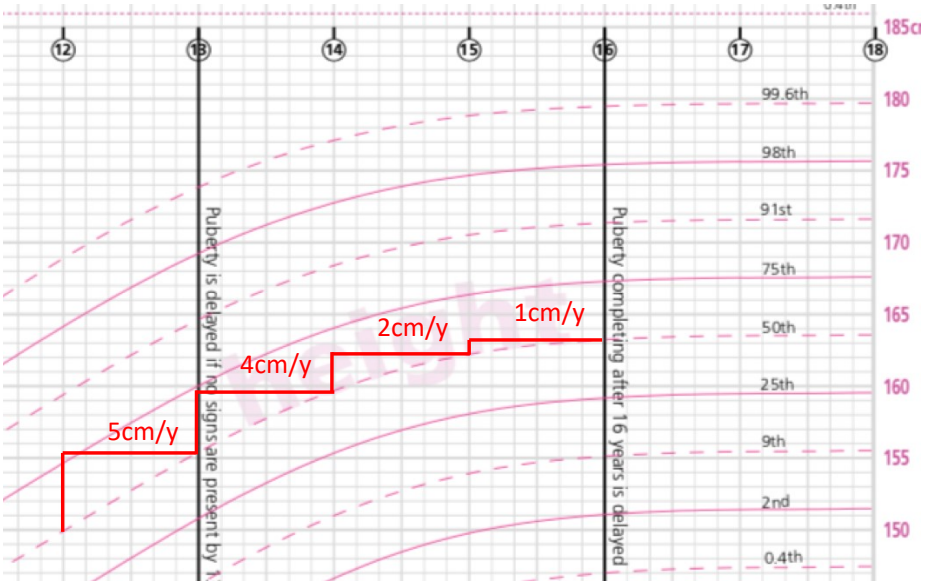
Costs associated with burosumab adverse events were included as suggested in the ERG report. In the ERG report an incidence rate of 28.2% for injection site reactions based on Study CL201 and Study CL205 was used. The rate used in the new version of the model is 38.3%.

2.1.3 Age at which treatment stops

In the previous version of the model it was assumed that growth stopped before the age of 17 in girls and before the age of 18 in boys. Clinical experts at the committee meeting indicated that measures of final height can be defined as a growth velocity that has slowed to less than a defined amount of <2cm per annum, in line with current guidelines around growth hormones. The company investigated this issue and presented RCPCH growth charts for girls and boys, respectively (see Figure 1 and Figure 2 below). According to the company, these charts suggest

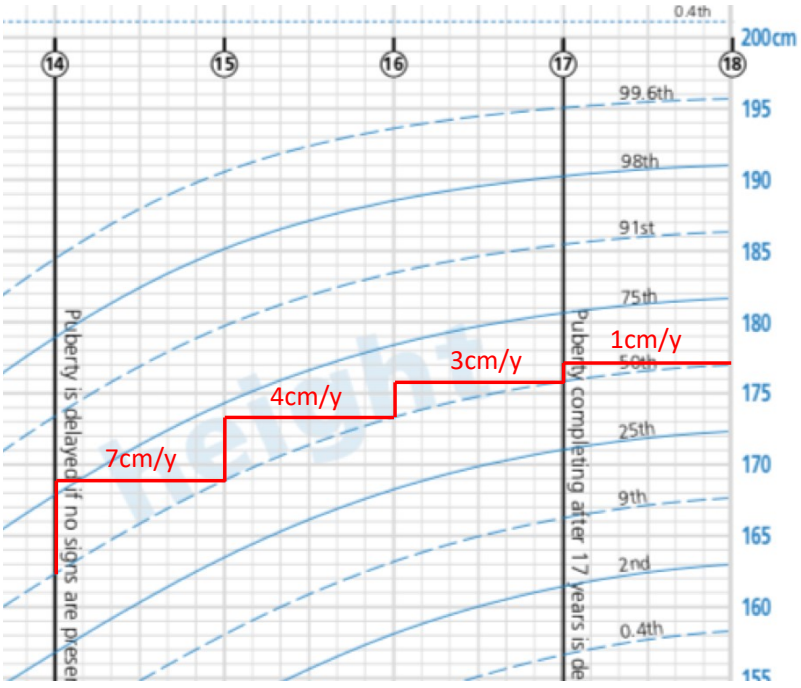
that growth slows to less than a defined amount of <2cm per annum before the age of 15 in girls and before the age of 17 in boys. Based on this, the company assumed that growth stopped at the age of 14 in girls and at the age of 16 in boys in the new version of the model. The company indicated that this was aligned to data submitted as part of the NICE TA188 for growth hormone, which indicated that treatment ceased between 14 and 16 years (Takeda et al. 2009).

Figure 1. UK growth charts will growth velocity, girls



Source: Figure 1 in Appendix B of the company's response to ECD.

Figure 2. UK growth charts will growth velocity, boys



Source: Figure 2 in Appendix B of the company's response to ECD.

ERG comment:

Based on the RCPCH growth charts presented by the company, and provided that there are no errors in them, the ERG disagrees with the choice of the age at which boys stopped treatment. Figure 2 shows that before the age of 17, growth velocity is 3cm per year. Therefore, 17 should have been chosen for boys as the age for stopping treatment. In case that this contradicts the data in Takeda et al. 2009, the ERG considers that the company should have been chosen the most conservative approach, which in this case it would be to assume an age of 17 for boys since the lower the age at which patients stopped treatment, the lower the ICER.

It is also unclear whether "a growth velocity that has slowed to less than a defined amount of <2cm per annum" should include 2cm or not. The notation using "<2cm" suggests that 2 cm should be included. If that is the case, then the age at which girls stopped treatment should be 15.

2.1.4 Utilities in childhood and adulthood

Utilities during childhood

In the revised analyses, the company did not adjust the utilities for missing values (as preferred by the committee). Instead of that the company re-contacted the clinical experts who reported missing values in an attempt to gain a full dataset. However, this was not possible for several reasons which are described in Appendix B of the company's response to ECD. From the utilities obtained during the original study of one clinical expert that had not provided a healed health state value, it was found that this expert had scored the mild and moderate health states with the highest possible value (1.0). Therefore, it can be inferred that this clinical expert would have scored the healed health state with 1 too. This information was included in the new version of the model and the impact of this missing value on the overall utilities can be seen in Table 10.

Table 10: Utilities by health state and age group

		Company submission (adjusted)	ERG (unadjusted)	Revised company submission (unadjusted)
Age 1-4	Healed rickets	0.872	0.800	0.834
Age 1-4	Mild	0.774	No change	No change
Age 1-4	Moderate	0.685	No change	No change
Age 1-4	Severe	0.546	0.610	0.610
Age 5-12	Healed rickets	0.969	0.890	0.909
Age 5-12	Mild	0.757	No change	No change
Age 5-12	Moderate	0.613	No change	No change
Age 5-12	Severe	0.521	0.602	0.602
Age 13+	Healed rickets	0.861	0.811	0.843
Age 13+	Mild	0.671	No change	No change
Age 13+	Moderate	0.575	No change	No change
Age 13+	Severe	0.462	0.479	0.479

Source: Table 10 in company's response to ECD (Appendix B).

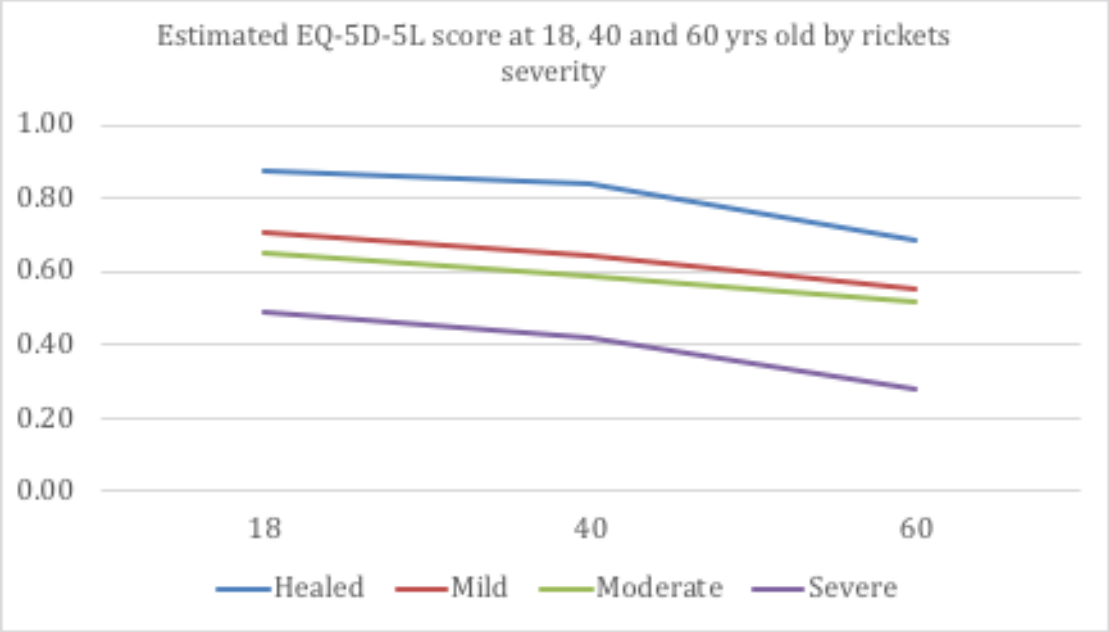
ERG comment:

The ERG agrees with the approach taken by company regarding the estimation of the utility for the Healed health state. However, it should be noted that the limitations (and hence the uncertainty) regarding the estimation of utilities discussed in the ERG report have not been resolved.

Long-term outcomes: Utilities during adulthood

The committee has acknowledged that there is lifetime benefit for people treated with burosumab because it can prevent irreversible bone damage, but have concerns that the long-term consequences of the progressive bone disease and ongoing metabolic symptoms of XLH, which would not be affected by burosumab, are uncertain. The committee considered that the ERG's approach to apply an arbitrary decrement at 20 years was purely illustrative of the potential effect of the assumption of disease stabilisation. To provide more estimates of long-term utilities rather than arbitrarily assuming a decline, a further study was conducted.

The company conducted an extension of the original vignette study with five UK clinical experts to elicit utilities for adults with different levels of XLH severity at different stages of adulthood. Each expert reviewed every case study, for which the participant had to imagine an adult in a pre-specified age group (18, 40 and 60 years old) with a level of XLH severity (severe, moderate, mild and healed rickets) and had to consider the impact on different aspects of HRQL using the EQ-5D-5L. Full details of the study are provided in Lloyd et al. 2018. A graphical representation of the utilities derived from the study is shown in Figure 3. A decline in HRQL from 18 to 60 years of age with increasing severity of rickets can be observed. It should be noted that the magnitude of the decline observed is greater than the decline in the quality of life of the general population (which can be attributed to co-morbidities associated with XLH disease progression, with the development of osteoarthritis, osteomalacia and other functional complications) but also that the decline was greatest in the severe health states, supporting the hypothesis that an aligned skeleton at the end of growth will result in fewer further complications during adulthood.



Source: Figure 4 in Appendix B of the company's response to ECD.

In particular, it was estimated that at the age of 40, patients that had healed rickets at the end of growth had a utility of 0.84 (compared to 0.89 in the general population) and at the age of 60, the estimated utility was 0.69 (compared to 0.82 in the general population). The utility declines estimated by the experts shown in Table 11 were applied in addition to the general population decline in quality of life in the new analyses presented by the company.

Table 11. Age-dependent utility multipliers associated with XLH derived from the vignette study by health state severity

Age (years)	Healed	Mild	Moderate	Severe
12 - 24	1.000	1.000	1.000	1.000
25-34	0.992	0.992	0.992	0.992
35-39	0.966	0.966	0.966	0.966
40-44	0.959	0.909	0.913	0.863
45-54	0.922	0.875	0.878	0.830
55-59	0.881	0.836	0.839	0.793
60-74	0.752	0.748	0.759	0.554
75+	0.689	0.686	0.696	0.508

Source: Table 11 in company's response to ECD (Appendix B). Note there are two tables captioned Table 11 in Appendix B; this refers to the first one.

Furthermore, the company included additional data from the RUDY database.

[redacted]

[redacted]

Table 12. EQ-5D-5L baseline utility scores stratified by age from XLH patients in RUDY

Age group	Age range	Observations	Mean	Std. Dev.	Min	Max
10	10-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	20-29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	30-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	50-59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	60-69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70	70-79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80	80-89	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 11 in company's response to ECD (Appendix B). Note there are two tables captioned Table 11 in Appendix B; this refers to the second one.

Figure 4. Correlation of EQ-5D-5L baseline utility scores and age from XLH patients in RUDY (n=40)

Source: Figure 6 in Appendix B of the company's response to ECD.

ERG comment:

The ERG could not find the extension of the original vignette study conducted by the company in the new submission of evidence. Therefore, the ERG cannot assess any aspects of this new study. Nevertheless, it should be noted that including the results of this new resulted in a scenario which is more favourable to burosumab than the original scenario considered by the company where no decline in health effects were considered. This is most likely due to the observed decline in utilities being greatest in the severe health state. The ERG considers that it is up to the clinical experts in the committee to decide whether this assumption is supported by clinical plausibility.

2.1.5 Patient Access Scheme

A patient access scheme (PAS) resulting in a [redacted] discount of burosumab original list price was applied in the company's revised analyses

2.2 Revised economic analyses results

The company's original base case resulted in an ICER of [redacted] with 16.9 undiscounted incremental QALYs. The revised economic analysis submitted by the company included the amendments described in the previous section. Following these amendments, the list price ICER was [redacted] with 15.53 undiscounted incremental QALYs. With PAS, the ICER is reduced to £76,996. Note that a discount rate of 1.5% was used by the company. Applying a 3.5% discount rate resulted in an ICER of £120,419 with the PAS.

2.2.1 Revised base-case results and scenario analysis

The results of the revised economic analysis are presented at list price in Table 13 and the new PAS price in Table 14. The incremental impact of each change between the original and revised model is shown, along with the following scenario analyses:

1. Use of a 3.5% discount rate.
2. Assuming treatment stops at the ages of 16 in girls and 17 in boys.
3. Including caregiver disutilities. A caregiver disutility of -0.08 was deemed a reasonable estimate of the disutility of a caregiver of an XLH patient as it was based on one caregiver of a patient with limited activity (Kuhlthau et al. 2010). The company assumed that this disutility would apply to patients in the moderate and severe health states up to the age of 18.
4. Most conservative scenario: use of a 3.5% discount rate, assuming treatment stops at the ages of 16 in girls and 17 in boys, no inclusion of long-term utility changes.

Table 13: Step-by-step modifications from original base case to revised base-case and additional scenarios (without PAS)

Scenario / change	Total costs (£)		Total QALYs		Incremental costs (£)	Incremental QALYs	ICER (£)	Undiscounted QALYs
	Burosumab	SoC	Burosumab	SoC				
Company original base case*	[redacted]	£50,580	36.29	25.99	[redacted]	10.30	[redacted]	16.89
Use of ERGs preferred method of calculation of transition probabilities and inclusion of adverse event costs for burosumab	[redacted]	£50,580	36.32	25.99	[redacted]	10.32	[redacted]	16.92
Include CL301 study data into transition probabilities	[redacted]	£50,675	36.31	26.23	[redacted]	10.08	[redacted]	16.52
Set the age at treatment termination in line with the stopping rule of growth velocity <2cm per year	[redacted]	£50,675	36.31	26.23	[redacted]	10.08	[redacted]	16.52
Revised utilities during childhood	[redacted]	£50,675	35.45	26.41	[redacted]	9.04	[redacted]	14.92
Apply progressive utilities during adulthood	[redacted]	£50,675	34.72	25.37	[redacted]	9.35	[redacted]	15.53
Final revised model at 1.5% discount rate	[redacted]	£50,675	34.72	25.37	[redacted]	9.35	[redacted]	15.53
Further scenario: Including caregiver disutilites	[redacted]	£50,675	34.66	24.88	[redacted]	9.78	[redacted]	15.99
Further scenario: 3.5% discount rate	[redacted]	£32,687	21.57	16.05	[redacted]	5.52	[redacted]	15.53
Conservative scenario - original model but with: use of ERGs preferred method of calculation of transition	[redacted]	£32,687	21.79	16.41	[redacted]	5.38	[redacted]	14.92

probabilities and inclusion of adverse event costs for burosumab Include CL301 study data into transition probabilities Revised utilities during childhood a 3.5% discount rate								
Source: Table 13 in company's response to ECD (Appendix B). *This is the model that was presented in response to the ERG clarification questions, which included the correction of minor errors								

Table 14: Step-by-step modifications from original base case to revised base-case and additional scenarios (with PAS)

Scenario / change	Total costs (£)		Total QALYs		Incremental costs (£)	Incremental QALYs	ICER (£)	Undiscounted QALYs
	Burosumab	SoC	Burosumab	SoC				
Company original base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Use of ERGs preferred method of calculation of transition probabilities and inclusion of adverse event costs for burosumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Include CL301 study data into transition probabilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Set the age at treatment termination in line with the stopping rule of growth velocity <2cm per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised utilities during childhood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply progressive utilities during adulthood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final revised model at 1.5% discount rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Further scenario: Including caregiver disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Further scenario: 3.5% discount rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conservative scenario as detailed in Table 13*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 14 in company's response to ECD (Appendix B). *Note that there is no Table 12 in Appendix B.

ERG comment:

The company has presented a number of scenarios to test the robustness of the ICER to changes on several assumptions. Given the new economic analyses results, it can be concluded that the ICER is not sensitive to:

- Including the results of the Phase 3 study (transition probabilities).
- ERGs preferred method of calculation of transition probabilities.
- Costs of adverse events associated with burosumab (as preferred by the ERG).
- Correction to the calculation of utilities during childhood.
- Including disutilities for caregiver.

On the other hand, the new analyses results indicated that the ICER is sensitive to:

- Age at which treatment is stopped.
- Long-term utilities in adulthood.
- Discount rate.
- Burosumab PAS price.

The ERG considers that there are still unresolved uncertainties associated to the first three items above. Uncertainty around the age at which treatment is stopped was discussed in Section 2.1.3. uncertainties regarding long-term utilities were discussed in Section 2.1.4. The company considers that the assessment of burosumab reflects the case for which the use of 1.5% discount is applicable since there are significant long-term benefits accruing over a patient's lifetime. In particular, the company claims that a discount rate of 1.5% should be used on the basis that burosumab meets the following criteria:

- Treatment enables patients to have a near full-health, where they otherwise would have had a very severely impaired life.
- This is effect is sustained across their lifetime (more than 30 years).
- It is highly likely that the long-term health benefits are likely to be achieved given the robust evidence on long-term outcomes presented in this submission.
- The treatment does not commit the NHS to significant irrecoverable costs.
- Burosumab assessment is comparable to the recent HST appraisal of Strimvelis (HST7), where the committee considered that it was likely that the 1.5% discounting rate was intended to cover situations when costs are incurred up-front, but benefits are accrued over a longer period. Furthermore, the 2018 release of the HM Treasury Green Book specifically states that QALYs should be discounted at a rate of 1.5%.

As with the original assessment of the original evidence, the ERG considers that it is up to the committee to decide whether the above statements are applicable to burosumab and therefore whether a discount rate of 1.5% or 3.5% should be applied.

In the next section, the results of additional scenario analyses conducted by the ERG are presented to illustrate the impact of the remaining uncertainties on the ICER.

2.2.2 Additional scenario analysis conducted by the ERG

The ERG conducted three additional scenarios and compared the results to the company's revised base case. The first scenario considered that the treatment stopping age is 15 for girls and 17 for boys. The second scenario assumed that the treatment effect of burosumab is stopped 20 years after treatment is stopped as in the ERG report. The third scenario considers a 3.5% discount rate on both costs and effects. The results are shown in Table 15. It can be seen that the ICER is sensitive to these three assumptions since in the all three scenarios the ICER increased significantly compared to the company's revised base case (17%, 55% and 56%, respectively).

Table 15: Additional scenarios conducted by the ERG (with PAS)

Scenario / change	Total costs (£)		Total QALYs		Incremental costs (£)	Incremental QALYs	ICER (£)	Change with respect to base case ICER (%)
	Burosumab	SoC	Burosumab	SoC				
Final revised model at 1.5% discount rate	**£770,966**	**£50,675**	**34.72**	**25.37**	**£720,291**	**9.35**	**£76,996**	
Stopping treatment age is 15 for girls and 17 for boys	£893,889	£50,675	34.72	25.37	£843,214	9.35	£90,136	+17%
ERG scenario stopping treatment effect after 20 years	£770,966	£50,675	32.44	26.41	£720,291	8.47	£119,325	+55%
3.5% discount rate	£697,171	£32,687	21.57	16.05	£664,484	5.52	£120,419	+56%

Appendix: Methodology of studies and baseline characteristics

Table A1: Methodology for studies CL201, CL002, CL205 and CL301

Study name	CL201	CL002	CL205	CL301
Objectives	• Identify a dose and dosing regimen of burosumab, based on safety and PD effect in paediatric XLH patients • Establish the safety profile of burosumab for the treatment of children with XLH including ectopic mineralisation risk, cardiovascular effects, and immunogenicity profile	To characterise change in rickets severity over time with conventional therapy (oral phosphate/active vitamin D) in children with XLH ages 5 to 14 years.	Primary objectives: • Establish the safety profile of burosumab for the treatment of XLH in children between 1 and 4 years old • Determine the pharmacodynamic (PD) effects of burosumab treatment on serum phosphorus and other PD markers that reflect the status of phosphate homeostasis in children between 1 and 4 years old with XLH Additional study objectives are to assess the following in children between 1 and 4 years old with XLH: • Effects of burosumab on rickets • Effects of burosumab on growth and lower extremity deformity • Pre-dose burosumab drug concentration levels	Evaluate the effects of burosumab on improving rickets, maximising growth, and restoring phosphorus homeostasis compared with active control (oral phosphate/active vitamin D therapy), as well as to evaluate the safety of burosumab, in children with XLH (aged 1 to ≤ 12 years) with confirmed evidence of rickets.

Study name	CL201	CL002	CL205	CL301
Location	This study is being conducted at a total of nine centres: four in the United States, three in the United Kingdom, one in France, and one in the Netherlands	Two sites in the USA.	This study is being conducted at 3 centres in the USA.	The study enrolled patients across [redacted]
Design	Randomised, multicentre, open-label, dose-finding Phase 2 study assesses the PD, efficacy, and safety of burosumab in prepubescent children (5 to 12 years old) with XLH. The study consists of two Screening Visits, a 16-week Titration Period, a 48-week Treatment Period, and a 96-week Treatment Extension Period.	Retrospective radiographic and medical chart review of patients with XLH who had longitudinal historical radiographs of the wrist, knee, or long leg taken between the ages of 5 and 14 years (inclusive).	Multi-centre, open-label, single-arm, Phase 2 study in children from 1 to 4 years old with XLH who are naive to therapy or have previously received conventional therapy with oral phosphate and active vitamin D to assess the safety, PD, PK, and efficacy of burosumab administered via subcutaneous (SC) injection Q2W for a total of 64 weeks.	Multicentre, randomised, open-label, Phase 3 study
Duration of study	The planned study duration is 160 weeks (approximately 3 years): 16 weeks in the Titration Period, 48 weeks in the Treatment Period, and 96 weeks in the Treatment Extension Period.	This is a retrospective study. The mean duration between baseline and post-baseline radiographs was [redacted] weeks]).	The planned duration of treatment in this study is 64 weeks. Patients who complete the study may continue into an extension study.	64 weeks: • Primary analysis is at Week 40 • Analyses at Week 64 will assess the durability of treatment effect, additional efficacy outcomes, and long-term safety Patients from either treatment groups who complete the active-controlled treatment period of the study (64 weeks) may be eligible for an

Study name	CL201	CL002	CL205	CL301
				extension study and receive burosumab treatment for up to an additional 96 weeks or until the study drug is commercially available.
Sample size and Patient population	Approximately 30 paediatric patients with XLH and radiographic evidence of bone disease ("pre-expansion patients") were planned for enrolment under the original study protocol. The study was expanded per amendment 3 of the protocol to include additional patients ("expansion patients") who were required to have rickets severity of at least 1.5 at the knee (per the Rickets Severity Score [RSS] method), for a total of approximately 50 patients planned overall.	[redacted] paired wrist and knee images) Children with a confirmed diagnosis of XLH who have radiographic images for at least two time points taken between the ages of 5 and 14 years.	Approximately 10 paediatric patients were planned for enrolment and 13 patients were enrolled. This submission summarises the planned, primary analyses of data to week 40 for all 13 patients and additional safety data available through the data cut-off date.	n = 61
Inclusion criteria	• Male or female, aged 5 – 12 years, inclusive, with open growth plates • Tanner stage of 2 or less based on breast and testicular development • Diagnosis of XLH supported by ONE of the following: o Confirmed PHEX mutation in the patient or a directly related family member with	• Male or female, with radiographic images from at least two time points taken between the ages of 5 and 14 years, inclusive • Diagnosis of XLH based on a confirmed PHEX mutation in the patient or a directly related family member with appropriate X-linked inheritance, or a clinical	• Male or female, aged ≥ 1 year and < 5 years • PHEX mutation or VUS in either the patient or a directly related family member with appropriate X-linked inheritance • Biochemical findings associated with XLH including serum phosphorus	• Male or female, aged 1 to ≤12 years with radiographic evidence of rickets with a minimum rickets severity score (RSS) total score of 2 as determined by central read • PHEX mutation or variant of uncertain significance in either the patient or in a

	appropriate X-linked inheritance o Serum FGF23 level > 30 pg/mL by Kainos assay • Biochemical findings (based on overnight fasting [minimum 4 hours] values collected at Screening Visit 2) associated with XLH including: o Serum phosphorus ≤ 2.8 mg/dL (0.904 mmol/L) o Serum creatinine within age-adjusted normal range • Standing height < 50th percentile for age and gender using local normative data. (Criterion was changed to "< 50th percentile" [from "< 25th percentile"] per Protocol Amendment 1) • Radiographic evidence of active bone disease including rickets in the wrists and/or knees, AND/OR femoral/tibial bowing, OR, for expansion patients, an RSS score in the knee of at least 1.5 points as determined by central read (The inclusion criterion of RSS ≥ 1.5 for patients enrolled with the expansion of the study was	diagnosis of XLH based on biochemical profile and clinical symptoms	< 3.0 mg/dL (0.97 mmol/L) and serum creatinine within age-adjusted normal range. (Criteria to be determined based on fasting [minimum 4 hours] values collected at baseline.) • Radiographic evidence of rickets; at least 5 patients will be required to have a RSS at the knee of at least 1.5 points as determined by central read • Willing to provide access to prior medical records for the collection of historical growth, biochemical, and radiographic data and disease history • Provide written informed consent by a legally authorised representative after the nature of the study has been explained, and prior to any research-related procedures • Must, in the opinion of the Investigator, be willing and able to complete all aspects of the study, adhere to the study visit schedule, and comply with the assessments	directly related family member with appropriate X-linked inheritance • Biochemical findings associated with XLH: Serum phosphorus <3.0 mg/dL (0.97 mmol/L) 4) Serum creatinine within age-adjusted normal range* • Serum 25(OH)D above the lower limit of normal (≥16 ng/mL) at the Screening Visit • Have received both oral phosphate and active vitamin D therapy for ≥ 12 consecutive months (for children ≥3 years of age) or ≥ 6 consecutive months (for children <3 years of age) prior to the Screening Visit

	added per Protocol Amendment 3) • Willing to provide access to prior medical records for the collection of historical growth, biochemical and radiographic data, and disease history • Provide written or verbal assent (if possible) and written informed consent by a legally authorised representative after the nature of the study has been explained, and prior to any research-related procedures • Must, in the opinion of the investigator, be willing and able to complete all aspects of the study, adhere to the study visit schedule and comply with the assessments • Females who have reached menarche must have a negative pregnancy test at Screening and undergo additional pregnancy testing during the study. If sexually active, male and female patients must be willing to use an acceptable method of contraception for the duration of the study. (This inclusion criterion added per Protocol Amendment 1)			

Study name	CL201	CL002	CL205	CL301
Exclusion criteria	• Use of a pharmacologic vitamin D metabolite or analog (eg, calcitriol, doxercalciferol, alfacalcidol, and paricalcitol) within 14 days prior to Screening Visit 2; washout took place during the Screening Period • Use of oral phosphate within 7 days prior to Screening Visit 2; washout took place during the Screening Period • Use of calcimimetics, aluminium hydroxide antacids, systemic corticosteroids, and thiazides within 7 days prior to Screening Visit 1 • Use of growth hormone therapy within 3 months before Screening Visit 1. (Criterion was changed to “within 3 months”	• Currently or previously treated with burosumab in Ultragenyx protocol UX023-CL201 (images and data from patients in the current study were collected as a part of UX023-CL201)	• Unwilling to stop treatment with oral phosphate and/or pharmacologic vitamin D metabolite or analog (eg, calcitriol, alfacalcidol) during the screening period and for the duration of the study • Presence of nephrocalcinosis on renal ultrasound grade 4 based on the following scale: o 0 = Normal o 1 = Faint hyperechogenic rim around the medullary pyramids o 2 = More intense echogenic rim with echoes faintly filling the entire pyramid o 3 = Uniformly intense echoes throughout the pyramid o 4 = Stone formation: solitary focus of echoes at the tip of the pyramid • Planned or recommended orthopaedic surgery, including staples, 8-plates or	• Tanner stage 4 or higher through physical examination • Height percentile >50% based on country-specific norms • Use of aluminium hydroxide antacids, systemic corticosteroids, acetazolamide, and thiazides within 7 days prior to the Screening Visit • Current or prior use of leuprorelin, triptorelin, goserelin, or other drugs known to delay puberty • Use of growth hormone therapy within 12 months before the Screening Visit • Presence of nephrocalcinosis on renal ultrasound grade 4 based on the following scale: o 0 = Normal o 1 = Faint hyperechogenic rim around the medullary pyramids

	[from "within 12 months"] per Protocol Amendment 2 • Use of bisphosphonates for 6 months or more in the 2 years prior to Screening Visit 1 • Presence of nephrocalcinosis on renal ultrasound graded ≥ 3 based on the following scale: o 0 = Normal o 1 = Faint hyperechogenic rim around the medullary pyramids o 2 = More intense echogenic rim with echoes faintly filling the entire pyramid o 3 = Uniformly intense echoes throughout the pyramid o 4 = Stone formation: solitary focus of echoes at the tip of the pyramid • Planned or recommended orthopaedic surgery, including staples, 8-plates or osteotomy, within the clinical trial period • Hypocalcaemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits (based on overnight fasting [minimum 4 hours] values collected at Screening Visit 2)		osteotomy, within the clinical trial period • Hypocalcaemia or hypercalcaemia, defined as serum calcium levels outside the age-adjusted normal limits. (Criteria to be determined based on fasting [minimum 4 hours] values collected at baseline.) • Presence or history of any condition that, in the view of the Investigator, places the patient at high risk of poor treatment compliance or of not completing the study • Presence of a concurrent disease or condition that would interfere with study participation or affect safety • History of recurrent infection or predisposition to infection, or of known immunodeficiency • Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to	o 2 = More intense echogenic rim with echoes faintly filling the entire pyramid o 3 = Uniformly intense echoes throughout the pyramid o 4 = Stone formation: solitary focus of echoes at the tip of the pyramid • Planned or recommended orthopaedic surgery (implantation or removal), including staples, 8-plates or osteotomy, within first 40 weeks of the study • Hypocalcaemia or hypercalcemia, defined as serum calcium levels outside the age-adjusted normal limits • Evidence of hyperparathyroidism • Use of medication to suppress PTH (e.g., cinacalcet, calcimimetics) within 2 months prior to the Screening Visit

	• Evidence of tertiary hyperparathyroidism as determined by the Investigator • Use of medication to suppress parathyroid hormone (PTH) within 2 months prior to Screening Visit 1 • Presence or history of any condition that, in the view of the investigator, places the patient at high risk of poor treatment compliance or of not completing the study • Presence of a concurrent disease or condition that would interfere with study participation or affect safety • Previously diagnosed with human immunodeficiency virus antibody, hepatitis B surface antigen, and/or hepatitis C antibody • History of recurrent infection or predisposition to infection, or of known immunodeficiency • Use of a therapeutic monoclonal antibody within 90 days prior to Screening Visit 1 or history of allergic or anaphylactic reactions to any monoclonal antibody • Presence or history of any hypersensitivity to burosumab		completion of all scheduled study assessments	• Use of any investigational product or investigational medical device within 30 days (within 4 months in Japan) prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments

Study name	CL201	CL002	CL205	CL301
	excipients that, in the judgment of the investigator, places the patient at increased risk for adverse effects • Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to completion of all scheduled study assessments			
Intervention (s) (n =) and comparator (s) (n =)	Burosumab, n=52: Pre-expansion Patients • Dose Cohort 1, n=10 (0.1 mg/kg Q2W [n=5], 0.2 mg/kg Q4W [n=5]) • Dose Cohort 2, n=10 (0.2 mg/kg Q2W [n=5], 0.4 mg/kg Q4W [n=5]) • Dose Cohort 3, n=16 (0.3 mg/kg Q2W [n=8], 0.6 mg/kg Q4W [n=8]) • Expansion Patients • Dose Cohort 3, n=16 (0.3 mg/kg Q2W [n=8], 0.6 mg/kg Q4W [n=8])	Not applicable (patients had been on conventional therapy for approximately 6 years prior to study enrolment).	Burosumab, n=13	• Open-label burosumab by subcutaneous injection (n = 29) • Oral Phosphate/Active Vitamin D (conventional therapy) - Active control (n = 32)
Baseline differences	Demographic characteristics were similar for patients randomised to	Not applicable	Not applicable	Demographic and baseline characteristics were similar across the treatment groups.

Study name	CL201	CL002	CL205	CL301
	the Q2W and to the Q4W dose regimens.			Patients in the conventional therapy arm had received prior conventional therapy for [redacted] patients in the burosumab arm; they were [redacted] and had started conventional therapy [redacted].
Duration of follow-up, lost to follow-up information	All patients completed at least 64 weeks on study. No patient discontinued from the study, and all patients are continuing in the study as of the data cut-off date.	Patients were not followed up as this was a retrospective study. The mean duration between baseline and post-baseline radiographs was [redacted])	All 13 patients were included in each analysis set (Efficacy Analysis Set, PK/PD Analysis Set, and Safety Analysis Set). As of the data cut-off date (20 April 2017), all patients completed week 40, no patient had discontinued from treatment or from the study, and all patients continue in the study. Additionally, 9, 7, and 4 patients have received burosumab through weeks 42, 44, and 46, respectively, as of the data cut-off date.	All subjects completed at least 40 weeks on study (primary analysis). A number of subjects have continued the study up to week 64 (results not yet available).
Statistical tests	No formal hypothesis was tested to compare treatment groups (Q2W and Q4W) in this study. Changes from baseline in efficacy parameters were tested. Statistical analyses were reported using summary tables, figures, and data listings. Statistical tests were	Retrospective radiographic, biochemical, growth, and conventional therapy data collected from all patients in this historical cohort were summarised by both event incidence and patient incidence. No formal	The planned sample size for this study of approximately 10 patients was considered appropriate to evaluate the burosumab dose and PK/PD relationship in children aged 1 to 4 years to confirm if that relationship is similar to that	The full analysis set (used for both efficacy and safety analyses) includes all randomised subjects who received at least one dose of assigned medication. For efficacy analyses, subjects are

Study name	CL201	CL002	CL205	CL301
	2-sided at the alpha=0.05 significance level, and 2-sided 95% confidence intervals (CIs) were used. All p-values were presented as nominal p-values. No adjustment on multiplicity was made. For the primary efficacy endpoint of change in RSS total score, the difference between the two dose regimens (Q2W and Q4W) was summarised with 95% CIs. For repeated measures, the generalised estimating equation (GEE) approach was used for assessing the change over time. The GEE model included regimen, study visit and interaction between regimen and study visit as categorical variables. Model-based estimates of changes from baseline and corresponding 95% CIs were provided along with P-values for assessing statistical significance. As exploratory analyses, covariates such as baseline measures, gender, and age were considered for adjustment within GEE models. Continuous variables were summarised with means, standard deviations (SD), standard errors (SE), medians, interquartile ranges	hypothesis was tested in this study. The primary evaluation in the current study was the change in rickets severity, as evaluated by 2 different methods (RSS and RGI-C). Rickets was assessed based on radiographic changes from radiograph pairs that were 1 to 2 years apart, with the earlier pair considered the baseline radiograph. For each radiograph pair, growth and biochemical data were linked to baseline and post-baseline radiographs by time of measurement and changes in growth and biochemical parameters were summarised. RSS, growth, and biochemical data were also summarised by event incidence in addition to paired incidence; the details of assessment plan for each endpoint are provided in. Subgroups were also prespecified based on rickets severity of the baseline radiographs: baseline radiographs with RSS total score ≥1.5 were referred to as the Higher RSS subgroup and those with RSS total score <1.5 were	observed in older children (aged 5–12 years; N=52) in Study UX023-CL201. Analyses groups included: the Safety Analysis Set (all patients who received at least one dose of study drug), the Efficacy Analysis Set (all patients who received at least one dose of study drug and have at least one post-study drug measurement), and the PK/PD Analysis Set (all patients who received at least one dose of study drug and have evaluable blood samples). Continuous variables were summarised with means, standard deviations (SDs), standard errors (SEs), medians, interquartile range, minimums, and maximums. Categorical variables were summarised by counts and by percentages of patients in corresponding categories. No imputation on missing data was made, unless stated otherwise. All data obtained from the case report forms (CRFs) as well as any derived	being analysed by the randomised treatment group. At Week 40 analysis (the primary efficacy analysis time point), the primary hypothesis of the primary endpoint is to test whether there is a difference between the burosumab and active control groups in the mean RGI-C global scores at Week 40. An Analysis of Covariance (ANCOVA) model with treatment group adjusting for baseline rickets severity and age was used to test this hypothesis at a two-sided alpha level of 0.05. The proportion of RGI-C responders (subjects with mean RGI-C global score >=+-2.0) was summarised for each treatment group. At Week 64 (additional analysis), RGI-C global score over time will be analysed using the repeat measurement model that includes treatment group, visit, treatment group by visit interaction, and

Study name	CL201	CL002	CL205	CL301
	(Q1, Q3), minimums, and maximums. Categorical variables were summarised by counts and by percentages of patients in corresponding categories. No imputation on missing data was made, unless stated otherwise. All data obtained from the Case Report Forms (CRFs) as well as any derived data were included in data listings. Efficacy results were analysed by subgroups defined by RSS total score at baseline. The "higher RSS" subgroup consisted of patients with RSS total scores at baseline ≥ 1.5; the "lower RSS" subgroup consisted of patients with RSS total scores at baseline < 1.5. The value of 1.5 was based on the median RSS total score of the study population at the interim analysis of the first 12 patients. Results also were analysed by subgroups defined by degree of functional impairment: for 6MWT results by percentage of predicted 6MWT (abnormal: < 80%, or normal range: ≥ 80%) at baseline, and for the POSNA-PODCI questionnaire by Global Functioning scale score	referred to as the Lower RSS subgroup. For continuous variables, the mean, standard deviation, median, quartiles, minimum, and maximum are provided; 95% confidence intervals (95% CI) on change from baseline were calculated for paired radiographs by one sample T test. For discrete data, frequency and percent distributions are used. Analysis was performed on the analysis sets by patient incidence, by radiograph incidence, or by paired radiographs.	data were included in data listings. Changes from baseline to post-baseline time points in PD and efficacy parameters were tested for statistical significance. Statistical tests were 2-sided at the alpha = 0.05 significance level and 2-sided 95% confidence intervals (CIs) were used. All p-values were presented as nominal p-values. No adjustment for multiplicity was made. An analysis of covariance (ANCOVA) model was applied to each RGI-C score (wrist, knee, global and lower limb deformity) and change from baseline in each RSS score (wrist, knee and total). The ANCOVA model for RSS scores included the change from baseline in RSS score as the dependent variable and age and RSS score at baseline as covariates. The ANCOVA model for RGI-C scores included the RGI-C score as the dependent variable and age and RSS at baseline as covariates.	adjusted for baseline rickets severity and age. The change from baseline in RSS total score over time will be analysed at Week 40 and Week 64 using the same method as that of the RGI-C global score.

Study name	CL201	CL002	CL205	CL301
	(abnormal: < 40, or normal range: ≥ 40) at baseline.		By-visit analyses using the Generalised Estimating Equations (GEE) model was applied for all PD parameters; the GEE model included change from baseline as the dependent variable, time as the categorical variable and adjusted for baseline measurement, with exchangeable covariance structure. By-visit analyses using the GEE model also was applied to recumbent length/standing height; the GEE model included the change from baseline as the dependent variable, visit and gender as factor, age and recumbent length/standing height z-score at baseline as covariates, with exchangeable covariance structure.	
Primary outcomes	Primary efficacy endpoint: Change from baseline in severity of rickets as measured by Rickets Severity Score (RSS) total score The primary efficacy analysis was at week 40. Additional efficacy analysis was carried out at week 64.	Conventional therapy endpoints include the following information: • Age at the time of initiating conventional therapy • Total duration of conventional therapy	The primary efficacy endpoint is the change from baseline in serum phosphorus.	Primary efficacy endpoint: Change from Baseline in severity of rickets as measured by RGI-C global score at Week 40.

Study name	CL201	CL002	CL205	CL301
Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy endpoints • Change from baseline in severity of rickets as measured by RSS knee and wrist scores • Change from baseline in the radiographic appearance of rickets and bowing as measured by Radiographic Global Impression of Change (RGI-C) global, knee, wrist and long leg scores • Growth (standing height, sitting height, arm length, and leg length) • Walking Ability (Six-minute Walk Test [6MWT]) • Functional disability and pain (Pediatric Orthopedic Society of North America – Pediatric Outcomes Data Collection Instrument [POSNA-PODCI])	• Conventional therapy treatment status at time of radiographic imaging (Yes/No) • Conventional therapy regimen at time of radiographic image taken, including medication • names, dose and frequency of administration for both phosphate and active vitamin D • Interruptions in conventional therapy of 3 months or more and reason for interruption Radiographic measures of rickets severity were assessed by Rickets Severity Scale (RSS) and Radiographic Global Impression of Change (RGI-C. Growth endpoints include standing height (length) in cm, z-score and percentile (adjusted by gender and age). Biochemical endpoints include change over time in serum or plasma phosphorus, calcium, iPTH, 1,25(OH)2D, and ALP corresponding to dates close to the date radiographic imaging was collected, where available.	• Change in rickets as assessed by the Radiographic Global Impression of Change (RGI-C) global score at weeks 40 and 64 • Change from baseline in RSS total score at weeks 40 and 64 • Change in lower extremity skeletal abnormalities, including genu varum and genu valgus, as determined by the RGI-C long leg score at weeks 40 and 64 • Change in recumbent length/standing height from baseline to post-treatment study time points in cm, height-for-age z-scores, and percentiles based on age and gender. • Historical growth records may be used to evaluate change in growth velocity Change and percentage change from baseline over time in serum alkaline phosphatase (ALP)	The key secondary endpoints include: • Change in lower extremity skeletal abnormalities as assessed by the RGI-C long leg score • Change from baseline in standing height/recumbent length Z score • Change from baseline in RSS total score • Change in serum phosphorus from baseline to mean post-baseline values • Change from baseline in ALP For the growth-related endpoints RGI-C long leg score and change from baseline in standing height/recumbent length Z score, the primary assessment time will be Week 64. For other key secondary endpoints, the primary assessment time will be Week 40. Because of the small sample size, no multiplicity will be adjusted

Study name	CL201	CL002	CL205	CL301
				for the key secondary endpoints. Other Secondary Endpoints include: • Rickets Endpoint(s) o Proportion of subjects with a mean RGI-C global score ≥ +2.0 (substantial healing) o Change in rickets as assessed by RGI-C wrist and knee scores o Change from baseline in RSS wrist and knee scores • Growth Endpoint o Change in growth velocity Z score from pre-treatment to post-treatment • PD Endpoint(s) o Change from baseline over time in serum phosphorus o Number of subjects reach the normal range of serum phosphorus (3.2 - 6.1 mg/dL) over time o Change from baseline over time in serum 1,25(OH)2D,

Study name	CL201	CL002	CL205	CL301
				urinary phosphorus, TmP/GFR and TRP • Pain, Fatigue and Physical Function Endpoint(s) o Change from baseline in the PROMIS (Patient-Reported Outcomes Measurement Information System) scores in Pediatric Pain Interference, Physical Function Mobility and Fatigue domains o Change from baseline in the Faces Pain Scale – Revised (FPS-R) Change from baseline in the Six Minute Walk Test (6MWT) total distance and percent of predicted normal
Source: CS, Tables 10 and 12, pages 66-70 and 75-77 and CS, Table 11, pages 71-73 and Table 1, page 3, Appendix A ECD Response				

Table A2: Demographic and baseline characteristics in studies CL002, CL201, CL002 and CL205

	Study CL002	CL201	CL205	CL301	
	Radiographic analysis set (n=35)	**Burosumab (n=26)**	**Burosumab (n=13)**	**Burosumab (n = 29)**	**Conventional therapy (n = 32)**
Age (years), mean (SD)	8.58 (2.57)[a]	8.7 (1.72)	2.9 (1.15)	[redacted]	[redacted]
Sex, male n (%)	11 (31.4%)	12 (46.2%)	9 (69.2%)	[redacted]	[redacted]
Race White Black/ African-American (CL301: Asian) Other	 34 (97.1%) 0 (0.0%) 1 (2.9%)	 23 (88.5%) 2 (7.7%) 1 (3.8%)	 12 (92.3%) 1 (7.7%) 0	[redacted]	[redacted]
Weight (kg), mean (SD)	NR	31.87 (7.92)	12.92 (1.81)	[redacted]	[redacted]
Height (percentile for age and gender), mean (SD) (CL301: Height in cm, mean (SD))	NR	[redacted]	[redacted]	[redacted]	[redacted]
Standing Height (z-score), mean (SD)	-1.89 (0.920)[a]	-1.72, 1.03	-1.38 (1.19)	[redacted]	[redacted]
Renal ultrasound score, (0 – 5 scale) – n (%) 0 1 2 3	NR	[redacted]	NR	[redacted]	[redacted]

	Study CL002	CL201	CL205	CL301	
	Radiographic analysis set (n=35)	Burosumab (n=26)	Burosumab (n=13)	Burosumab (n = 29)	Conventional therapy (n = 32)
Number (%) of Patients Who Received Prior Conventional Therapy	NA (100% received)	24 (92.3%)	13 (100%)	[redacted]	[redacted]
Duration of Prior Conventional Therapy, mean (SD)	> 6 years	7.02 (2.14) years	16.7 (14.39) months	[redacted]	[redacted]
Age When Conventional Therapy Was Initiated (years), mean (SD)	2.22 (1.768)	[redacted]	[redacted]	[redacted]	[redacted]
Pharmacodynamic parameters, mean (SD)					
Serum Phosphorus, mg/dL	NR	[redacted]	[redacted]	[redacted]	[redacted]
TmP/GFR (mg/dL)	NR	[redacted]	[redacted]	[redacted]	[redacted]
Serum 1,25(OH)2 D (pg/mL)	NR	[redacted]	[redacted]	[redacted]	[redacted]
ALP (U/L	NR	[redacted]	[redacted]	[redacted]	[redacted]
Rickets Severity					
RSS Total Score, mean (SD)	1.40 (0.747)[a]	1.92 (1.17)	2.92 (1.37)	[redacted]	[redacted]

Source: CS, Table 13, page 82 and Table 3, Appendix A, Response to ECD.
a) At baseline paired radiograph (the earlier radiograph pair)

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Burosumab for treating X-linked hypophosphataemia

ADDENDUM

This document contains the results of two scenarios produced by the ERG in response to the request made by the chair of the appraisal committee following the second evaluation committee meeting.

The revised economic analysis submitted by the company prior to the second committee meeting included the following specification:

- AE costs (at a frequency of 38.3%)
- ERG transition probability corrections
- CL301 data
- New childhood utilities
- Progressive utility decline (vignette extension)
- Stopping age of 14 and 16 for girls and boys respectively
- 1.5% discount rate

With the PAS, the ICER was £76,996. The following additional changes were requested by the chair to produce Scenario 1:

- Applying a 3.5% discount rate
- Original stopping age (16 and 17 for boys and girls respectively)

The following additional changes to Scenario 1 were requested to produce Scenario 2:

- Stopping age of 14 and 16 for girls and boys respectively
- Carer disutility

Table 1: Amendments requested by committee chair post – committee meeting 2

Scenario / change (additional changes)	Total costs (£)		Total QALYs		Incremental costs (£)	Incremental QALYs	ICER (£)	Undiscounted QALYs		
	Burosumab	SoC	Burosumab	SoC				Burosumab	SoC	Incremental
Company revised analysis prior to meeting 2	[redacted]	£50,675	34.72	25.37	[redacted]	9.35	£76,996	55.46	39.93	15.53
Scenario 1	[redacted]	£32,687	21.57	16.05	[redacted]	5.52	£149,565	55.46	39.93	15.53
Scenario 2	[redacted]	£32,687	21.51	15.61	[redacted]	5.52	£112,517	55.40	39.41	15.99