in collaboration with:

Erasmus School of Health Policy & Management

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Burosumab for treating X-linked hypophosphataemia

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual accuracy check. The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
14, 102, 112, 129, 130	Correction of typographical error: [redacted]
15, 125, 130	Correction of typographical error: [redacted]
23	Text deleted: Clinical heterogeneity, which the CS highlights has been frequently reported for XLH patients, is a core issue that may impact burosumab treatment. Some patients with a PHEX mutation who are diagnosed with XLH retain residual gene activity. In practical terms, this may mean that further dose-titrations are necessary that take into consideration not just weight but also residual gene activity. It is unclear if there is a validated test available to determine PHEX activity.
27	Text deleted: Since the aetiology and pathophysiological mechanisms behind XLH remain largely unknown, the mechanism-of-action of burosumab must be considered as ameliorating the symptoms rather than treating the underlying cause.
65	Text changed to: Additional work on clinical effectiveness undertaken by the ERG has been included in section 4.3.2 of this report.
74,75	Section Equity weighting removed from Table 5.1.
95	Text deleted: These revisions have been included in the revised base-case.
109	Text added: Note that this CI (and the ones shown below) is based on the standard deviation instead of the standard error and therefore it is incorrect. These CI's are used to illustrate the way the company included the uncertainty into the model.

Multiple sources of evidence were used to inform the parameters of the economic model. The proportion of males/females at baseline, the initial distribution of patients per disease severity stratified by age and the transition probabilities for burosumab were derived from the clinical studies CL201 and CL205. Transition probabilities for the SoC arm were derived from a UK chart review in the base-case analysis and from the study CL002 in a scenario analysis. General population weight data (UK growth charts) were used for the weight distribution. Mortality rates were obtained from the national life tables for England, for the period 2014 to 2016, as published by the Office of National Statistics. Utility values for the health states of the model were derived from a vignette study conducted by the company. Additionally, age specific multipliers were used based on the general population.

The price of burosumab was provided by the company. Burosumab is available in 10 mg, 20 mg and 30 mg vials. In the CS, it was stated that the Summary of Product Characteristics (SmPC) recommends dose rounding to the nearest 10 mg. Based on this assumption, annual patient costs by age and weight were estimated in the base-case analysis. Resource use for burosumab monitoring was based on expert opinion, while unit costs were taken from NHS reference costs. Standard of care treatment costs were estimated based on the dose recommended in clinical guidelines and the summary of product characteristics. Unit costs were taken from the British National Formulary (BNF). Resource use for surveillance costs was based on expert opinion and unit costs were taken from NHS reference costs. Physiotherapy resource use was based on published literature and complemented by expert opinion. Unit costs taken from PSSRU. A number of different sources were used for the estimation of orthopaedic intervention costs. Resource use was based on the prevalence observed in CL201, published literature and expert opinion. Unit costs were mostly sourced from the NHS reference costs, except the unit costs for osteotomy, which were based on published literature. A deterministic one-way sensitivity analysis was conducted for key clinical and economic parameters in the model. A probabilistic sensitivity analysis was also conducted. A number of scenario analyses were also performed to assess the robustness of the model results to changes in structural assumptions made by the company.

The company's analysis estimated that patients treated with burosumab gained 10.304 more discounted quality adjusted life years (QALYs) compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When discounting was not applied, the estimated gain in QALYs was 16.891 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

1.7 Summary of the ERG's critique of the value for money evidence submitted

The CS states that a systematic review search was undertaken for economic, cost and resource use and HRQoL evidence using a combined search for all of these areas. The company submission and response to clarification provided sufficient details for the ERG to appraise the literature searches. Of main concern to the ERG was the narrow search conducted, which included few XLH synonyms and an unnecessarily restrictive use of study design filters.

The ERG identified several issues in the company's analyses. The ERG main concerns were related to the method used by the company to estimate the transition probability matrices for burosumab, the source of utilities used by the company and the assumption of lifelong treatment effects of burosumab. The choice of the discount rate was also challenged by the ERG.

The results of the ERG base-case resulted in an ICER increased by [redacted] compared to the company's base-case ICER. Most of the total increase in the ICER (despite the effect of applying the 3.5% discount rate) was due to assuming a treatment effect duration for burosumab of 20 years instead of lifelong as

assumed by the company. The ERG also conducted a new probabilistic sensitivity analysis (PSA) and additional scenario analyses exploring the impact of choosing prior distributions for the burosumab transition matrices. The latter was proven to be crucial and in the several scenarios provided by the ERG, the ICER ranged from [redacted] to [redacted].

Based on the ERG results, it is expected that, from the payer perspective, the decision uncertainty related to burosumab value for money would be low, given that the ICER estimates from all ERG analyses are above the acceptable thresholds considered for orphan drugs and the burosumab cost effectiveness probability at such thresholds was [redacted].

1.8 Summary of the evidence submitted on the impact of the technology beyond direct health benefits and on the provision of specialised services

A budget impact model to estimate the costs to the NHS for a period of five years of adopting burosumab in England was also included in the CS. The results presented by the company suggested that the net budget impact of implementing burosumab (with an estimated prevalence of [redacted] patients) will be [redacted] in the first year and will rise to [redacted] in the fifth year. The cost of burosumab at year 5 amounts to [redacted]. The estimated total number of patients eligible for burosumab treatment after five years is [redacted] and the uptake of burosumab rises from 40% in year 1 to 90% in year 5.

The CS did not include any estimates of costs (savings) or benefits incurred outside of the NHS and PSS associated with of burosumab. The company indicated that at this stage this was not possible to quantify. However, the company expects significant savings to patients through healing of rickets and overall reduction or elimination of symptoms with burosumab.

1.9 Summary of the ERG's critique on the evidence submitted on the impact of the technology on non-health related benefits

The ERG considers the assumptions made in the budget impact analysis questionable. There are concerns about the theoretical population size and the expected uptake rate of burosumab in England. In the CS, it was reported that the size of the patient population [redacted] is not expected to change over time. This estimate is based on an assumption that the patients are only treated if they have growing skeletons. In the CS, it was stated that XLH is not associated with an increased risk of death, compared to the standard population. The potential (and theoretical) population size is assumed to remain constant.

Since real-world data suggest that there could be [redacted] XLH patients between one and 17 years of age in England, using the estimate of [redacted] children and assuming a 40% uptake in Year 1, followed by 65% uptake in Year 2 and a 90% uptake thereafter would equate to [redacted] children in year 1, [redacted] children in Year 2 and [redacted] children thereafter being treated with burosumab. The cost of burosumab at year 5 would then amount to [redacted]. The company indicated that burosumab is not expected to require additional resources to enable treatment administration, as it will be delivered via homecare. Homecare provision for XLH is being organised and funded by the company and will therefore not have any additional financial or resource impact on the NHS.

The ERG considers it inadequate that the impact of XLH on costs (savings) or benefits incurred outside of the NHS and personal social services associated with of burosumab was not identified prior to the submission to NICE.

presumed from this value that the remaining 60-75% of patients with well-controlled XLH achieve normal growth rates with conventional therapy. Other research has indicated that height velocity commonly increases during the first year of conventional therapy, and after two years of successful treatment, can be restored to its maximal potential in the majority of patients, although adult height usually remains compromised.[3, 23]

Dental disease in XLH patients is highlighted in the CS with a study by Anderson 2012 that assesses 53 patients with hypophosphataemic rickets.[21] Sixteen out of 53 patients were <18 years of age and therefore represent the population of interest for the burosumab indication described in the CS. Of these 16 patients, the mean number of endodontically affected teeth was 0.3 (standard deviation (SD) 0.9), while the median number was 0 (first and third quartile: 0.0 and 0.0). No comparisons were provided either in the referenced study, in the CS[1] or in the company's response to clarification letter (question A17[2]) for the number of endodontically affected teeth that would be expected in a healthy age-matched population. Based on the current information, the need for endodontic treatment among paediatric HR patients cannot be considered comprehensive, although it appears clear that dental issues are prevalent in adult XLH patients.

2.2.6 Diagnosis

Diagnosis of XLH is typically based on clinical findings, radiographic findings, biochemical testing and family history. Family history remains critically important to the early recognition of inherited forms. Although, genetic testing is increasingly used to confirm the diagnosis of XLH, radiographs have been the gold standard for the diagnosis and evaluation of rickets for several decades.[18, 40-42] The radiographic characteristics of rickets include lucency in the metaphyses, physeal widening, fraying and cupping.[6, 42] These diagnostic radiographic features of rickets typically reflect the impaired mineralisation and ossification affecting the growth plate. Bone manifestations are best seen in the metaphyses of rapidly growing bones, including the distal radius and ulna, distal femur, proximal and distal tibia and proximal humerus.[6, 42]

Paediatric patients with XLH are managed by paediatric endocrinologists and paediatric nephrologists. There are a limited number of expert clinicians with the necessary training and experience in rare metabolic bone diseases to appropriately manage children with XLH. It is anticipated that treatment would be initiated and monitored by specialist centres and clinicians.

2.2.7 Prognosis

As an update from the CS, which stated that no empirical evidence documenting the impact of XLH on mortality has been identified and that XLH is not thought to have an impact on the life expectancy of patients, a new analysis provided in the company's response to clarification letter stated that [redacted].[2]

ERG comment: The original statement (that XLH had no impact on life expectancy) was unlikely to be accurate given the extensive pathological manifestations associated with the disease. The updated

phosphate). Normalising phosphate levels is reported to ameliorate the bone-related symptoms (e.g. rickets) associated with XLH.

2.5 Current usage in the NHS

Burosumab is not currently in use in the NHS. The MHRA granted burosumab a 'Promising Innovative Medicine' (PIM) designation on 31 January 2017, and the EMA awarded burosumab conditional marketing authorisation on 23 February 2018. Burosumab is expected to be used in line with the anticipated marketing authorisation in children and adolescents with XLH from the age of one year old who have radiographic evidence of bone disease.
Burosumab is a monotherapy, meaning oral phosphate and vitamin D analogue therapy should be discontinued one week prior to initiation of treatment. Concurrent use of oral phosphate and vitamin D analogues is contraindicated with burosumab. Burosumab is administered every two weeks by subcutaneous injection.

Clinical expert opinion has suggested that patients responding well to burosumab treatment are likely to have a diminishing frequency of consultant visits over the longer term. In addition, burosumab will either prevent or improve skeletal abnormalities, and reduce the need for corrective surgery. Routine treatment with burosumab should also remove the need for additional supplementation with growth hormone in a small subset of patients where this is required.

The following ongoing monitoring is recommended with burosumab (Summary of Product Characteristics (Crysvita), 2017):[50]

- Monitoring for signs and symptoms of nephrocalcinosis, e.g. by renal ultrasonography, is recommended at the start of treatment and every six months for the first 12 months of treatment, and annually thereafter.

- Monitoring of plasma alkaline phosphatases, calcium, PTH and creatinine is recommended every six months (every three months for children 1- 2 years) or as indicated. Monitoring of urine calcium and phosphate is suggested every three months. Patient's fasting serum phosphate level should be monitored due to the risk of hyperphosphataemia. To decrease the risk for ectopic mineralisation, it is recommended that fasting serum phosphate is targeted in the lower end of the normal reference range for age. Dose interruption and/or dose reduction may be required.

- Increases in serum parathyroid hormone have been observed in some XLH patients during treatment with burosumab. Periodic measurement of serum parathyroid hormone is advised.

The high burden of frequent monitoring when the drug is first introduced will tail off once the patient is on a stable dose, and the overall burden of monitoring is expected to be reduced compared with that required for conventional therapy.

ERG comment: Kyowa Kirin aim to treat a paediatric and adolescent population of XLH patients from 1-17 years of age who have radiographic evidence of bone disease. After the age of approximately 17, when growth plates fuse, it is indicated that burosumab will be discontinued as it will no longer be required to stabilise rickets symptoms. Based on the therapeutic target of burosumab (FGF23) and the largely unknown pathological mechanisms of XLH, there is no evidence presented that burosumab therapy in childhood has long-term therapeutic consequences in adulthood following treatment cessation. Bone metabolism is an ongoing and dynamic process that will continue to be subject to the pathological consequences of hypophosphataemia. Thus, the ERG considers it unlikely that the diverse pathologic and phenotypic consequences of XLH will be ameliorated without therapeutic intervention

ERG comment: As there was no direct or indirect evidence available to compare burosumab with conventional therapy using evidence from RCTs, the evidence in the CS is based on a comparison of data from two single arm studies. Although the burosumab evidence is from a phase 2 trial, there was no control group and the randomisation was between different regimens of burosumab. The data for conventional therapy was obtained from a historical cohort study, which was different to the burosumab trial in terms of inclusion criteria and patient population. In order to try and adjust for differences between these two studies the company performed additional analyses which matched the two groups using propensity score matching. However, these analysis methods have major limitations, in that the matching can only include those variables measured in both studies. Randomisation in a clinical trial creates balanced group for both measured and unmeasured variables. In observational studies, the most important factors which are predictive of the outcome may not have been measured and any treatment comparisons using observational study data may be biased.[58]
The company only included three variables in the PSM, age, gender and RSS total score at baseline. The rationale for variable selection was not provided other than whether they seemed similar or not between the two study populations. No details were provided of how this similarity was judged. The ERG found no statistically significant differences in age and gender between the two groups and considered that only including three variables in the creation of the propensity scores may have been too few. Although the PSM groups were closer at baseline for these three variables compared to the original data, the results of the PSM analyses were very similar to those from a naïve comparison between the two study populations.

The company provided the statistical analysis programs used for the PSM analyses in the response to the clarification letter but not the data. Therefore, the ERG could not check the PSM analyses to establish that they could reproduce the results. Three different PSM methods were used and although they provided similar results it is not clear which PSM result should be considered the most reliable. The PSM analyses were only performed for rickets and not for any other relevant clinical or safety outcomes.

Due to the lack of a direct comparison between burosumab and conventional therapy and the limitations of using propensity score matching with data from two different observational studies the results of the rickets analyses presented by the company should be considered with caution. The results from CL301, a randomised controlled trial comparing the efficacy and safety of burosumab with active control (oral phosphate/active vitamin D therapy) in children with XLH (aged one to ≤12 years) are expected [redacted]. These will provide more reliable estimates for the clinical effectiveness and safety of burosumab compared to conventional therapy and should be given greater consideration than the naïve and adjusted analyses presented in the company submission.

4.4 Summary of evidence presented in other submissions

No other scientific evidence was submitted by other consultees.

4.5 Additional work on clinical effectiveness undertaken by the ERG

Additional work on clinical effectiveness undertaken by the ERG has been included in section 4.3.2 of this report. In addition, we will discuss the longitudinal review of patient records from three expert UK centres to provide additional data (n=43) commissioned by Kyowa Kirin as a UK alternative to CL002 which was a US study. The company provided a synopsis with details on the rationale, methodology and results of this UK study as part of the response to the clarification letter.[2]

of systematic oral phosphate supplements and active vitamin D analogues in the form of alfacalcidol A, or oral or injectable calcitriol.

The economic evaluation was conducted from the perspective of the NHS and PSS in England. The model estimates cost and health consequences over a lifetime time horizon for a cohort of patients with XLH aged one to 12 years at the beginning of the simulation. The cycle length of the model is one year. The outcomes of the model are the estimated incremental QALYs, the incremental costs and the incremental cost effectiveness ratio (ICER) associated with burosumab vs. SoC for treating XLH. Cost and health outcomes are discounted at a rate of 1.5%.

ERG comment: The scope of the economic evaluation is generally in line with the scope developed by NICE. Deviations in the company's decision problem were discussed in section 3.3 of this report. The adherence of the scope of the economic evaluation to the NICE reference case was also assessed by the ERG, and it is shown in Table 5.1 below.

Table 5.1: Adherence to the reference case principles relevant to highly specialised technologies

Element of economic analysis	Reference case	ERG comment
Defining the decision problem	The scope developed by NICE	The scope of the economic evaluation is generally in line with the scope developed by NICE. Deviations were discussed in Section 3.3 of this report.
Comparator	Therapies routinely used in the NHS, including technologies regarded as the current best practice	Standard of care (SoC) is the only comparator considered. It is the established clinical management without burosumab (systematic oral phosphate supplements and active vitamin D analogues in the form of alfacalcidol A, or oral or injectable calcitriol).
Perspective on costs	NHS and PSS	NHS perspective was adopted.
Perspective on outcomes	All health effects on individuals.	Patient health benefits were included in the model. Benefits to other afflicted individuals (e.g. caregivers) were not included in the model but discussed qualitatively in the company's submission (CS Chapter 14).
Type of economic evaluation	Cost-effectiveness analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Based on a systematic review	Meta-analysis was not used, as there is no direct or indirect evidence of the effectiveness of burosumab vs. SoC available. Effectiveness data was

Element of economic analysis	Reference case	ERG comment
		obtained from single-arm studies.
Measure of health effects	QALYs and life years	Health benefits are valued in terms of life years and QALYs gained.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	No, the utility values associated with the model's health states were derived from a vignette study conducted with 6 UK XLH clinical experts. The valuation was based on EQ-5D, which is the NICE standard.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects.	No, costs and outcomes were discounted at 1.5%.

5.3.2 Model structure

An Excel-based Markov model was developed by the company to perform the economic evaluation of burosumab for treating XLH patients in the UK. The model simulates the disease progression of XLH by using the Rickets Severity Score (RSS) as a surrogate for disease severity, which defines the different health states of the model, in patients treated with either burosumab or SoC. The impact of the disease is translated to lifetime costs and QALYs in the submitted cost effectiveness model. The model consists of four (mutually exclusive) health states representing different rickets severity levels (healed, mild, moderate, and severe) and a death state. The severity levels are defined based on the RSS, a radiographic scoring method developed to assess the severity of nutritional rickets. It scores abnormalities in the wrists and knees and is defined on a scale between 0 and 10. Healed rickets correspond to an RSS equal to 0, mild rickets correspond to an RSS between 0.5 and 1.0, moderate rickets correspond to an RSS between 1.5 and 2.0, and severe rickets correspond to an RSS larger or equal than 2.5. Transitions from every alive health state to any other alive health state are allowed in the model. Additionally, patients can move from any of the alive health states to the death state. The relation between the RSS and HRQoL and the choice of cut-offs on the RSS to define meaningful health states was based on a consensus from clinical experts. Figure 5.2 provides the graphical representation of the conceptual model as presented by the company.

Adverse event costs
No costs associated with AEs were used in the base-case analysis. In the sensitivity analysis, the impact of including costs associated with AEs (lower limit £0 and upper limit £5) were explored, using an incidence rate of 28.2% for injection site reactions based on Study CL201 and Study CL205.

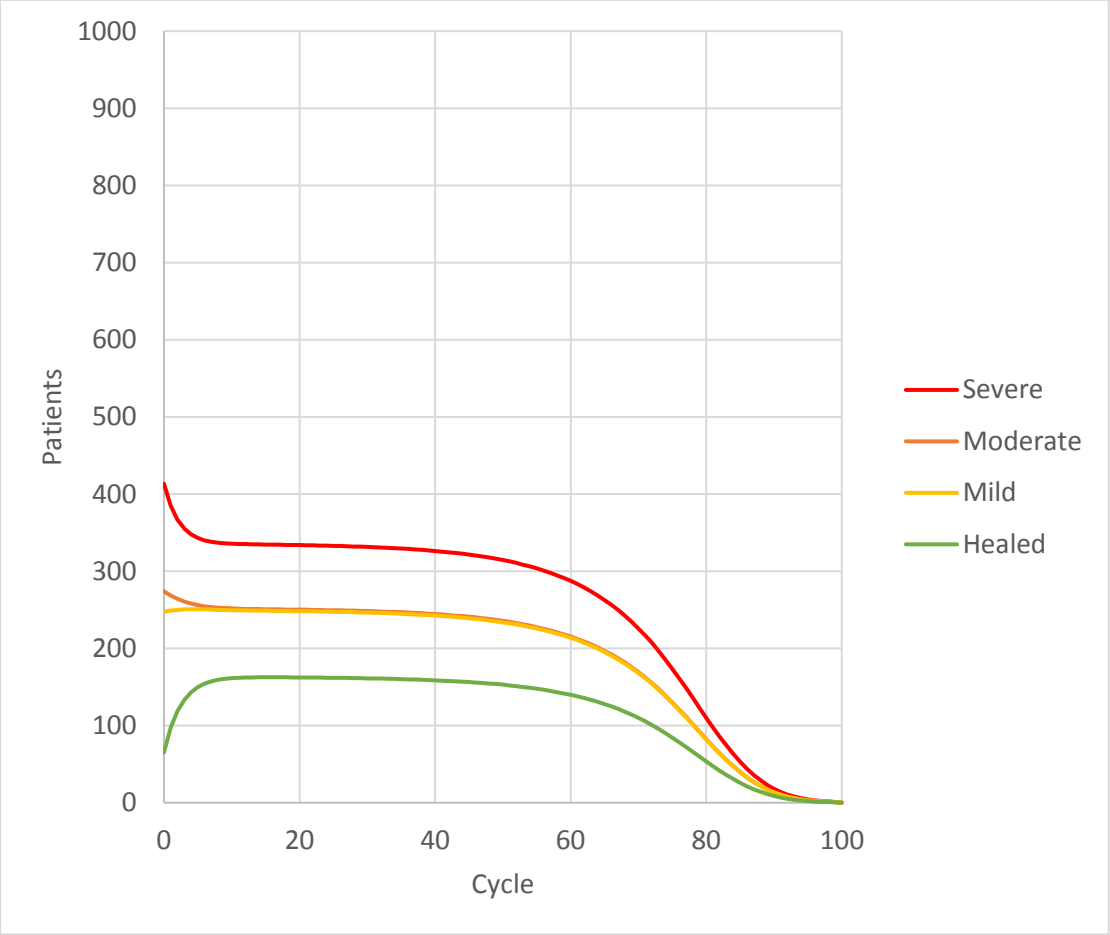
ERG comment: The company indicated that all known costs and resources have been considered. The ERG requested clarification of the orthopaedic intervention costs which are only considered to occur in patients with a rickets score of 1.5 or higher, but no evidence was provided for the relevant cut-off. In the CL, it was indicated that orthopaedic interventions are only required in patients that have a need for such intervention, who are mostly likely to have more severe rickets. The assumption (confirmed by clinical experts) states that if a patient has healed or mild rickets, then it is unlikely that they would require orthopaedic interventions. The ERG also indicated that the monitoring costs are applied only in the first year of treatment (for dose adjustments). Patients up to the age of 17 are expected to see a specialist every three months, regardless of whether they receive SoC or burosumab. This is incorporated into the surveillance costs which are incurred by all patients. These consultations with clinical specialists are to monitor the disease and treatment. The company indicated that after the first three months, burosumab is not expected to require any additional monitoring over that already conducted with SoC. The ERG indicated that treatment costs of the comparator are not age specific, but an average treatment cost for all patients age one to 17 is used in the model. Given that the comparator consists of two treatments, only one of which has a cost that is age-related (alfacalcidol) and the cost of alfacalcidol is not a driver of costs, the simplification of an average cost (instead of age specific) is acceptable. The revised model sent after the clarification phase comprised updated costs that reflect the same year (2016/17). Overall, the applied changes did not have an impact on the results. Surveillance costs are applicable to all patients and orthopaedic intervention costs are not drivers of the results.

In addition, the ERG had two priority questions in the CL about dosing and vial sharing of burosumab. The company indicated that vial sharing is not applied to burosumab. According to the company, if patients received their exact dose as per their weight, which could be a proxy scenario for vial sharing, the ICER would become [redacted]. Based on the SPC, if a patients' weight indicates a dose of 7.5 mg, then this will be rounded up to 10 mg. It was further stated that when patients are five years old, the calculated dose is 14.8 mg but the recommended dose to be administered is 10 mg. The recommended starting dose regimen in children, according to the CS, is based on experience in Study CL201 and Study CL205. Rounding to the nearest 10 mg was used during dose titration in Study CL201. The company indicated that when pharmacokinetic (PK) modelled dose levels were rounded to the nearest 10 mg a difference in dose of <5 mg is not expected to affect response. The maximum dose of 90 mg is recommended based on PK simulations and the practical limitation of a tolerable injection volume. It was stated that this information was presented to the EMA.

5.3.3.5 Demographic parameters included in the model

A number of demographic characteristics were considered in the model as input parameters. These included the initial distribution of patients per health state stratified by age (see Table 35 and Table 36 in the CS[1]) and the percentage of males (50.77%) at baseline. These parameters were obtained by combining the data from CL201 (all doses) and CL205. Weight by age and

Figure 5.1: Base-case: SoC Markov trace



Source: Electronic model (after clarification).[2]

5.4.1 Headline total QALYs and total costs for burosumab versus standard care

Table 5.14 presents the results of the cost effectiveness analysis of burosumab versus SoC for the base-case scenario.

Table 5.2: Summary results of the company's base-case scenario

	Costs	QALYs	ICER	Costs	QALYs	ICER
	Discounted			Undiscounted		
SoC	[redacted]	25.989	--	[redacted]	41.786	--
Burosumab	[redacted]	36.293	[redacted]	[redacted]	58.677	[redacted]

Source: Electronic model (after clarification).[2]
Abbreviations: ICER = incremental cost-effectiveness ratio, QALYs = quality-adjusted life years, SoC = standard of care

The company's analysis estimated that patients treated with burosumab gained 10.304 more discounted QALYs compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When no discounting was applied, the estimated gain in QALYs was 16.891 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

Tables 5.15 and 5.16 below present a breakdown of discounted QALYs and costs for burosumab and SoC. The company's analysis suggests that under burosumab patients accrue more than 95% of the total QALYs in the "Healed rickets" health state (least severe state),

Figure 5.2: Cost effectiveness acceptability curves

Figure redacted - CIC

Source: Figure 10 in response to clarification letter.[2]

ERG comment: The PSA analyses were well-performed in general and the ERG agrees with most of the choices regarding probability distributions made by the company.

After clarification, the ERG detected an error in the model, which was using the standard deviation instead of the standard error when sampling random values for the utilities. The company used the following approach to obtain random utilities for the PSA: first a utility for the moderate health state is randomly drawn from a Beta distribution, with parameters estimated from the mean and standard deviation values obtained in the vignette study. That utility value for the moderate health state is then used as reference and the utilities for the other health states are calculated by randomly drawing the difference in utility compared to the moderate health state from a Normal distribution, with mean and standard deviation also obtained in the vignette study. For example, for patients aged 13 years and older (note that these utilities are applied in the model until patients die, thus for a large number of model cycles) the estimated mean utility in the moderate health state is 0.575 and 95% confidence interval (CI) is (0.417,0.727). Note that this CI (and the ones shown below) is based on the standard deviation instead of the standard error and therefore it is incorrect. These CI's are used to illustrate the way the company included the uncertainty into the model. In order to calculate utilities for the mild health state, a random value is drawn from a Normal distribution with mean 0.096 (the estimated mean difference in utility in the mild health state compared to the moderate health state) and standard deviation 0.11. With these parameters, a 95% confidence interval for the difference in utility in the mild health state compared to the moderate health state is (-0.085,0.277). Likewise, a 95% CI for the difference in utility in the healed and severe health states compared to the moderate health state is (0.018,0.364) and (-0.378,0.152), respectively. However, the company made a further assumption when modelling the utilities which was bounding the sampled utilities so that the health states with less severe rickets get always a higher or equal utility value compared to the next more severe health state (i.e. healed ≥ mild ≥ moderate ≥ severe). The ERG does not agree with this assumption as will be explained below. This assumption results in practice in

provided, it was not mentioned for example what kind of internal validation tests were conducted. A detailed discussion on the face validity of the results was missing in the CS and the response to the clarification letter. Given the lack of cost effectiveness studies on XLH, the ERG feels that additional attention on the face validity of the results would have been helpful in this case. The ERG also asked the company to include in the response to the clarification letter the results of the ongoing external validation indicated on page 167 of the CS but these were not reported.

5.5 Discussion of available evidence relating to value for money for the NHS and PSS

Chapter 5 of this report focused on the economic evidence for burosumab submitted to NICE by the company. The company presented a QALY-based cost effectiveness model-based analysis comparing burosumab with SoC. The company's analysis estimated that patients treated with burosumab accumulated 10.304 more discounted QALYs compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When no discount was applied, the estimated gain in QALYs was 16.891 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

The ERG identified several issues in the company's analyses. The most important concerns were related to the operationalisation of "full recovery" in the healed rickets health state and lifelong burosumab treatment effect and the choice of the utilities for the base-case. These seemed to bias the results in favour of burosumab. The choice of the discount rate also had a significant impact on the model's results, as shown by the company in one of the scenarios they conducted. The ERG was also concerned about some of the assumptions made by the company in their PSA since these also seemed to bias the results in favour of burosumab.

Other issues discussed by the ERG were the difference of the effects of burosumab on patients younger than age five and patients older than age five, the method used by the company to estimate transition probability matrices, the choice of baseline weight, age and disease severity distribution, and the lack of any treatment/disease related adverse events. However, all these were proven to have a minor impact on the model's results.

Some of the problems identified within the critical appraisal of the economic analyses were addressed by the ERG in the next chapter of this report. Thus, the next chapter outlines the additional analyses conducted by the ERG, which includes the development of a new base-case analysis (including a PSA) and several additional scenarios.

for physiotherapy to manage the long-term consequences attributed to XLH. In the CS, these have not been factored in the budget impact analysis given its short time horizon.

7.2 ERG critique of the company's budget impact analysis

The ERG considers the assumptions made in the budget impact analysis questionable. There are concerns about the theoretical population size and the expected uptake rate of burosumab in England. In the CS, it was reported that the size of the patient population [redacted] is not expected to change over time. This estimate is based on an assumption that the patients are only treated if they have growing skeletons. In the CS, it was stated that XLH is not associated with an increased risk of death, compared to the standard population.[85] The potential (and theoretical) population size is assumed to remain constant.

Since real-world data suggests there could be [redacted] XLH patients between one and 17 years of age in England (see response to clarification letter – Question A4),[2] using the estimate of [redacted] children and assuming a 40% uptake in Year 1, followed by 65% uptake in Year 2 and a 90% uptake thereafter would equate to [redacted] children in year 1, [redacted] children in Year 2 and [redacted] children thereafter being treated with burosumab. The cost of burosumab at year 5 would then amount to [redacted]. The company indicated that burosumab is not expected to require additional resources to enable treatment administration, as it will be delivered via homecare. Homecare provision for XLH is being organised and funded by the company and will therefore not have any additional financial or resource impact on the NHS.

In study CL201, one patient experienced serious TEAEs, and [redacted]). 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]

Adverse events of treatment with conventional therapy have not been reported. Therefore, it is not possible to assess the relative safety and toxicity in relation to the comparator.

9.2 Statement of principal findings – cost-consequence evaluation, NHS budget impact and societal analysis

9.2.1 Cost-consequence analysis

The company conducted a systematic review of cost effectiveness studies of burosumab and other studies including costs, resource use and any HRQoL measure associated with XLH. A total of eight full-text studies were assessed for eligibility which were included in the final evaluation of evidence. However, none of these studies were deemed relevant to the economic evaluation of burosumab.

The company's deterministic analysis estimated that patients treated with burosumab accumulated 10.304 more discounted QALYs compared to SoC at an additional cost of [redacted], resulting in a cost per QALY of [redacted]. When no discount was applied, the estimated gain in QALYs was 16.891 at an additional cost of [redacted], resulting in an ICER equal to [redacted].

The ERG identified several issues in the company's analyses. The ERG main concerns were related to the method used by the company to estimate the transition probability matrices for burosumab, the source of utilities used by the company, and the assumption of lifelong treatment effects of burosumab. The latter was expected to have a major impact on the model results. The choice of the discount rate was also challenged by the ERG. Furthermore, given the limited evidence in this submission, the ERG highlighted the extra importance of the probabilistic results. In light of these issues, the ERG performed a new base-case analysis and a number of additional scenarios.

The results of the deterministic ERG base-case resulted in an ICER increased by [redacted] compared to the company's base-case ICER. Most of the total increase in the ICER (despite the effect of applying the 3.5% discount rate) was due to assuming a treatment effect duration for burosumab of 20 years. The ERG also conducted a new PSA and additional scenario analyses exploring the impact of choosing prior distributions for the burosumab transition matrices. The latter was proven to be crucial and in the several scenarios provided by the ERG, the probabilistic ICER ranged from [redacted] to [redacted]. Other scenarios explored by the ERG like using the utilities reported in Table 31 of the CS, rounding up the burosumab dose or bounding the utilities in the PSA were shown to have a minor to moderate impact on the model results.

Based on the ERG results, it is expected that, from the payer perspective, the decision uncertainty related to burosumab value for money would be low, given that the ICER estimates from all ERG analyses are

above the acceptable thresholds considered for orphan drugs and the burosumab cost effectiveness probability at such thresholds was [redacted].

9.2.2 Cost to the NHS and PSS

A budget impact model to estimate the costs to the NHS for a period of five years of adopting burosumab in England is also included in the CS. The results presented by the company suggested that the net budget impact of implementing burosumab (with an estimated prevalence of [redacted] patients) will be [redacted] in the first year and will rise to [redacted] in the fifth year. The cost of burosumab at year 5 amounts to [redacted]. The estimated total number of patients eligible for burosumab treatment after five years is [redacted] and the uptake of burosumab rises from 40% in year 1 to 90% in year 5. When a prevalence of [redacted] is considered by the ERG (with the same uptake rates), the estimated total number of patients eligible for burosumab treatment after five years reaches to [redacted]. The cost of burosumab at year 5 would then amount to [redacted].

9.2.3 Non-health benefits

The CS did not include any estimates of costs (savings) or benefits incurred outside of the NHS and personal social services associated with of burosumab. The company indicated that at this stage this was not possible to quantify. However, the company expects significant savings to patients through healing of rickets and overall reduction or elimination of symptoms with burosumab.

The ERG considers it as inadequate that the impact of XLH on costs (savings) or benefits incurred outside of the NHS and personal social services associated with of burosumab was not identified prior to the submission to NICE.

9.3 Strengths and limitations

9.3.1 Strengths of the CS

The ERG is confident that all relevant studies (published and unpublished) of burosumab were included in the CS, including data from ongoing studies. The same applies to the historical control patients. A control study in UK patients was mentioned in the CS without any results being report in the CS. However, results were provided as part of the response to the clarification letter. The reporting of outcomes from included studies also seems complete.

A range of relevant economic information was incorporated in the CS, including a QALY-based cost effectiveness model and an assessment of the expected costs to the NHS and PSS in England.

9.3.2 Weaknesses of the CS

The main limitation of the efficacy data reported in the CS is the study design of the included studies. Due to the absence of a control group in most studies it is not possible to make any direct comparisons between burosumab and conventional therapy. As stated by the company, the "burosumab phase 2 studies were uncontrolled dose finding or single arm studies, therefore an indirect comparison was not feasible" (CS, page 123).[1]

For children between one to four years old, only one study is presented in which all children received burosumab (CL205, N=13). A comparison with "established clinical management without burosumab" is not possible in this group of patients.

For children between five to 12 years old, the CS presents a study in which all children received burosumab (CL201). In addition, the CS presents a control study (CL002) in which children aged