BUR-CL207: An open-label, multicentre, non-randomised study to assess the safety, tolerability, pharmacokinetics and efficacy of burosumab in paediatric patients from birth to less than 1 year of age with XLH

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INTRODUCTION

- X-linked hypophosphataemia (XLH) is a hereditary disorder caused by genetic variants in the phosphate-regulating endopeptidase homolog X-linked (*PHEX*) gene that increase serum fibroblast growth factor 23 (FGF23) concentrations, leading to phosphate wasting, chronic hypophosphataemia and rickets/osteomalacia[1,2]
- Early initiation of treatment in children with XLH is known to improve height and prevent skeletal deformities, and may also improve dental and musculoskeletal outcomes[1,3,4]
- Burosumab is a recombinant fully human immunoglobulin G1 monoclonal antibody licensed by the European Medicines Agency for the treatment of XLH in children aged >1 year and adults[1,5,6]
- By selectively inhibiting FGF23, burosumab improves serum phosphate and active vitamin D levels as well as radiographic evidence of rickets severity, and has previously demonstrated significantly improved clinical outcomes in children with XLH aged 1–12 years compared with those continuing on conventional therapy[1,3,6–8]
- The safety profile assessed in clinical trials is favourable for burosumab; the most common adverse reactions reported in children with XLH aged >1 year across three clinical trials included injection-site reactions, headache, cough and pyrexia[3,7,8]

AIM

- This is a multicentre, open-label, non-randomised phase I/II study designed to evaluate the safety, tolerability, pharmacology and efficacy of burosumab in paediatric patients aged <1 year

STUDY METHOD

- This study is currently enrolling (in Europe only) and will include approximately 20 infants with XLH (<1 year old) with confirmed PHEX genetic variants
- Infants receiving conventional therapy will discontinue medications >1 week before commencing burosumab treatment and for the duration of the study
- All enrolled patients will receive burosumab (the trial does not contain a placebo arm), across three cohorts
- The duration of treatment will be 48 weeks, with a follow-up 8 weeks after completion of treatment on study – enrolled patients will be offered long-term follow-up in the Kyowa Kirin Registry upon consent
- A Data Safety Monitoring Board will review safety and efficacy data accrued in each cohort after completion of 4 weeks of treatment by the last enrolled patient, and additionally on an *ad hoc* basis throughout the study if deemed appropriate
- The study commenced with cohort 1; as no safety issues were identified in at least three patients enrolled after at least 4 weeks of treatment, cohorts 2 and 3 were initiated in parallel (Figure 1)

TRIAL DESIGN

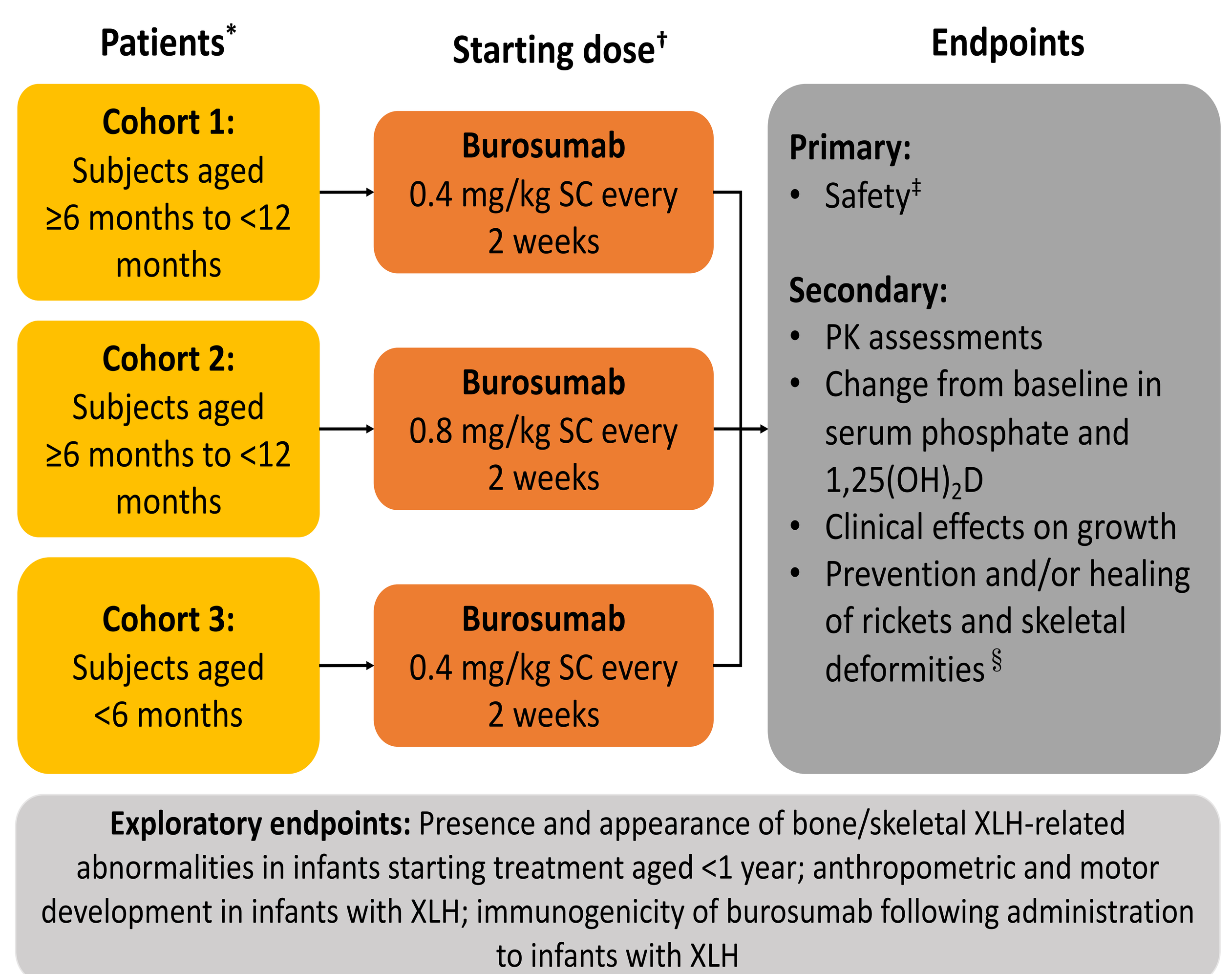

Figure 1: Trial design for BUR-CL207 including patient populations, treatment schedules and endpoints.

*Final number per cohort will depend on ages of eligible patients as enrolled – at least 20 infants are to be enrolled in total.

†Burosumab dose adjustments will be determined by monitoring serum phosphate levels – intra-subject dose titration within each cohort will be considered on a case-by-case basis and will depend on the individual subject's response to treatment. Burosumab dose may be escalated by 0.4 mg/kg up to a maximum of 2.0 mg/kg every 2 weeks if not clinically contraindicated, to reach serum phosphate levels above age-specific LLN. Hyperphosphataemia will be closely monitored, and burosumab doses may be decreased if necessary.

‡Incidence, frequency and severity of AEs and SAEs, including clinically significant changes in laboratory, physical examinations, vital signs, ECGs and imaging assessments (echo, RUS, X-ray) from baseline to scheduled time points (measured throughout the study up to week 48), and dose-limiting toxicities.

§ Change from baseline in radiographic appearance of rickets as assessed by the RGI-C scoring system at week 48. Change from baseline in rickets severity assessed by Rickets Severity Score at week 48. Change from baseline in lower extremity skeletal abnormalities as determined by RGI-C long leg score at week 48.

INCLUSION CRITERIA

1. Male or female paediatric subjects, aged <1 year.
2. *PHEX* mutation or variant of uncertain significance in either the subject or a directly related family member with appropriate X-linked inheritance.
3. Serum phosphate levels below the age-specific LLN at screening.

EXCLUSION CRITERIA

1. Unable to stop treatment with oral phosphate and/or pharmacological active vitamin D metabolite or analogue for at least 1 week before planned treatment start and for the duration of the study.
2. Patients born before 37 weeks of pregnancy with a chronological age of <6 months of age.
3. Impairment of renal function.
4. Presence of nephrocalcinosis on renal ultrasound.
5. Hypocalcaemia or hypercalcaemia.
6. Presence of a concurrent disease or condition that would interfere with study participation or affect subject safety.
7. Predisposition to infection or known immunodeficiency.
8. Severe dermatological conditions over the available injection sites.
9. Use of any investigational product or investigational medical device within 30 days prior to screening, or requirement for any investigational agent prior to study completion.
10. Metabolic bone disease, nutritional rickets and/or osteopenia of other origin than XLH at screening and/or baseline.
11. Serum levels of 25-hydroxyvitamin D below the LLN that are clinically significant in the opinion of the investigator.
12. Evidence of any hyperparathyroidism not associated with XLH as determined by the investigator.

STUDY STATUS

7	8	4	7
sites recruiting	sites set up	patients enrolled	participating countries

Figure 2: Current study status of the BUR-CL207 trial.

SUMMARY

- This study is actively recruiting in Europe; further enrolment of patients who meet the inclusion criteria at one of the participating sites will allow further research of burosumab in the treatment of infants aged <1 year, offering a potentially life-changing therapy option for these patients

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CONTACT INFORMATION

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$1,25(OH)_2D$, 1,25-dihydroxyvitamin D; AE, adverse event; ECG, electrocardiogram; echo, echocardiography; FGF23, fibroblast growth factor 23; LLN, lower limit of normal; *PHEX*, phosphate-regulating endopeptidase homolog, PK, pharmacokinetics; RGI-C, Radiograph Global Impression of Change; RUS, renal ultrasound; SAE, serious adverse event; SC, subcutaneous; XLH, X-linked hypophosphataemia.

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