



X-Linked Hypophosphatemia (XLH) Case Study: A Dynamic Development Model for Rare Disease

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Dynamic Development Approach

- Collaborative effort with FDA DBRUP to advance the development of burosumab for the treatment of XLH
- Comprehensive development program led to FDA approval in April 2018
 - June 2016: BTD granted based on interim data from a Phase 2 randomized, open-label study designed to identify the optimal dose and regimen for phosphate control
 - June 2017: Permission granted at pre-BLA meeting to file based on available pediatric and adult data with a pediatric Phase 3 active comparator group study to be completed as a PMC
- Focus today: strategies used to maximize data collected from the first pediatric study

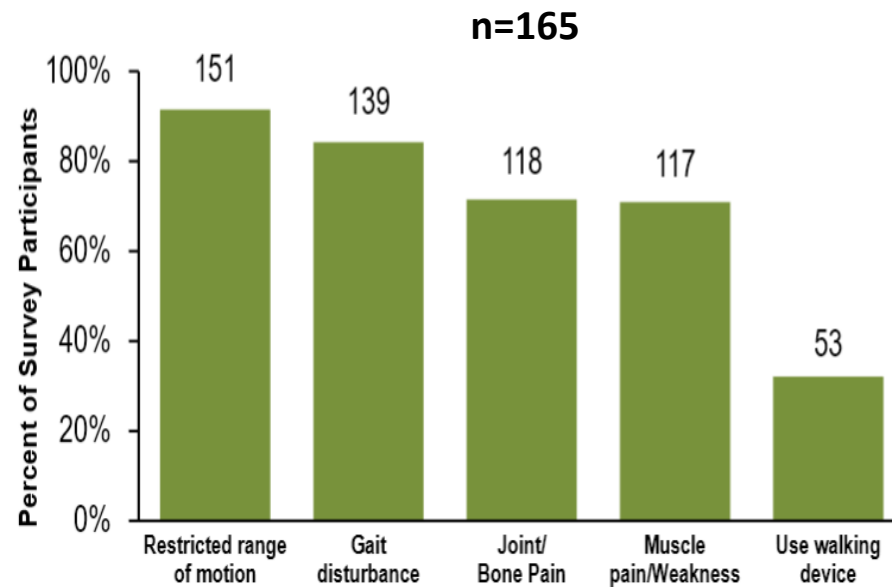
X-Linked Hypophosphatemia (XLH)

- Lifelong disorder of phosphate metabolism due to renal phosphate wasting that causes chronic hypophosphatemia
- Manifests in childhood as rickets, delayed growth and lower extremity deformity
- Progresses through adulthood leading to osteomalacia, frequent, poorly healed fractures, spinal stenosis, enthesopathy, osteoarthritis
- Disease causes pain and disability in children and adults
- Children treated with regimen of oral phosphate and active vitamin D analogues that requires careful monitoring
 - Efficacy is limited but enough to make placebo-controlled study unethical in children, particularly in early stage of investigation

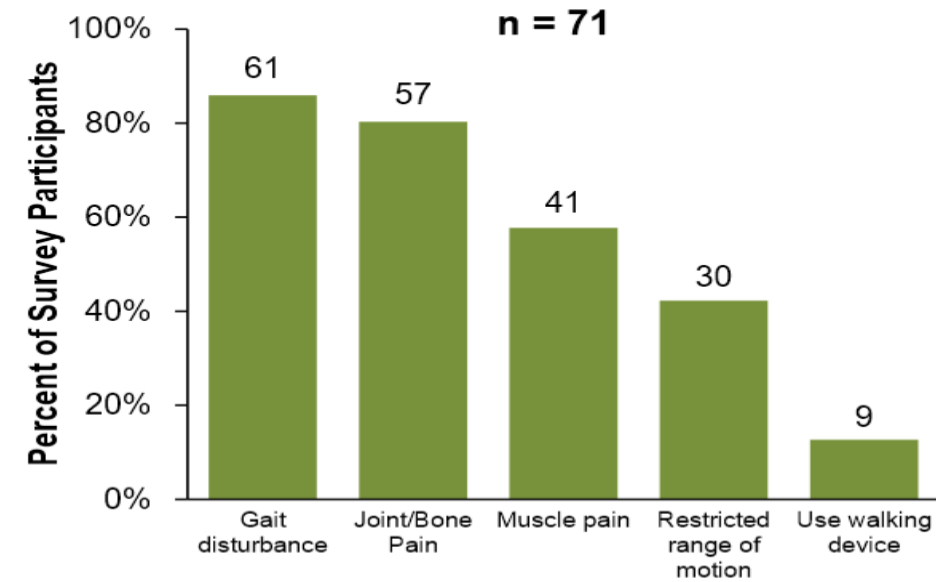
Learned about the Disease from the Patient Perspective Before Starting Trials

- Online survey conducted in partnership with patient association to provide insight into clinical presentation and impact of XLH on affected children and adults
 - Summary report provided to FDA as part of BTDA application
- Pain and gross motor impairment secondary to rickets and leg deformity identified as significant issues for children
- Bone pain, joint stiffness and mobility impairment secondary to osteomalacia and fractures were problems for adults
- 6MWT, BOT-2 and POSNA PODCI chosen as endpoints for children
- BPI-Q3, WOMAC Stiffness and Physical Function chosen as key secondary endpoints for adults
- Adult subjects randomized based on BPI-Q3 (pain at its worst)

Functional Limitations and Pain Are Common in Children and Adults Living with XLH



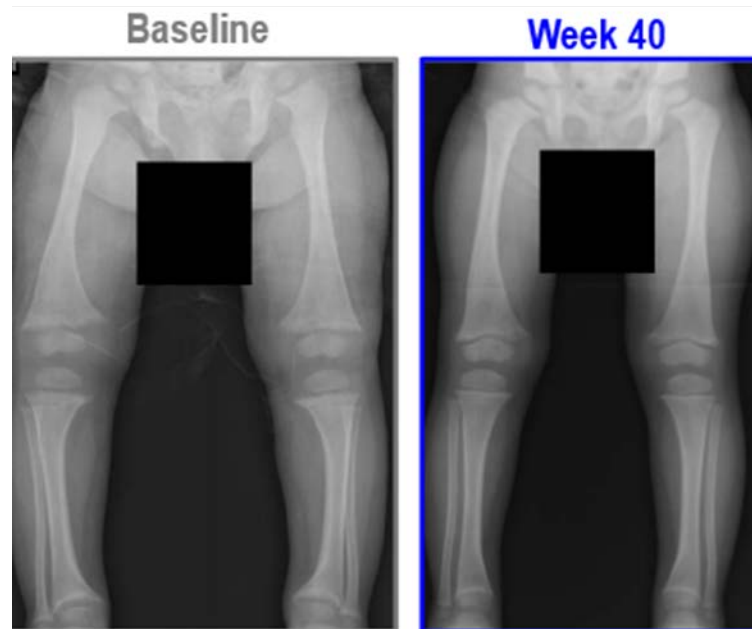
Reference: Skrinar A et al. X- Linked Hypophosphatemia (XLH) Impairs Skeletal Health Outcomes and Physical Function in Adults. Poster presented at: Endocrine Society's annual meeting; 5-8 Mar 2015; San Diego, CA



Reference: Linglart A et al. Impaired Mobility and Pain Significantly Impact the Quality of Life of Children with X- Linked Hypophosphatemia (XLH). Poster presented at: Endocrine Society's annual meeting; 1-3 Oct 2015; Barcelona, Spain

Developed and Validated Disease-Specific Measures to Evaluate Treatment Response

- Disease-specific radiographic global impression of change scale (RGI-C) developed and validated for use in XLH
 - Thacher (RSS) developed for nutritional rickets validated for XLH
- RGI-C readers rate a list of XLH-specific abnormalities in pre- and post-images and assign regional change scores for the wrist, knee and leg, as well as an overall impression score
- Abnormalities rated were chosen by pediatric radiologists
- Rater training conducted by a third party to ensure consensus on nomenclature, appearance and severity of abnormalities
- Intra-rater and inter-rater reliability established for RSS and RGI-C
- Relationship between RSS score, RGI-C score and biochemical and clinical measures established as part of validation



RATING OF LOWER LIMB DEFORMITY

How would you rate the change in XLH-related lower limb deformity? *Circle one*

-3	-2	-1	0	+1	+2	+3
Severe Worsening	Moderate Worsening	Minimal Worsening	No Change	Minimal Healing	Substantial Healing	Complete or Near Complete Healing

Identify abnormalities in image **A** on the left and then rate any change seen in image **B** on the right compared to image **A**

SINGLE ABNORMALITY RATING

STANDING LONG LEG	NOT in "A"	VARUS	VALGUS	DECREASED	UNCHANGED	INCREASED
L Tibia	☐	☒	☐	☒	☐	☐
R Tibia	☐	☒	☐	☒	☐	☐
L Fibula	☐	☒	☐	☐	☒	☐
R Fibula	☐	☒	☐	☐	☒	☐
L Femur	☐	☒	☐	☒	☐	☐
R Femur	☐	☒	☐	☒	☐	☐

Employed Strategies to Adjust for Lack of Placebo Arm

- XLH natural history study data mined to establish disease course in patients managed with conventional therapy and to evaluate potential for use as a comparator group
 - Radiographs, growth and lab data collected from ~100 children 5-14 years managed by an XLH expert
- Objective endpoints selected to allow subjects to serve as their own control
 - Radiographs and growth for children and biopsies for adults
- Blinding exercises used to enhance robustness of open-label study
 - Raters utilized for radiographic ratings and biopsy endpoints were blinded to subject ID, gender, age and treatment status
 - Radiographs from natural history study were randomly mixed with clinical trial images to further blind the raters

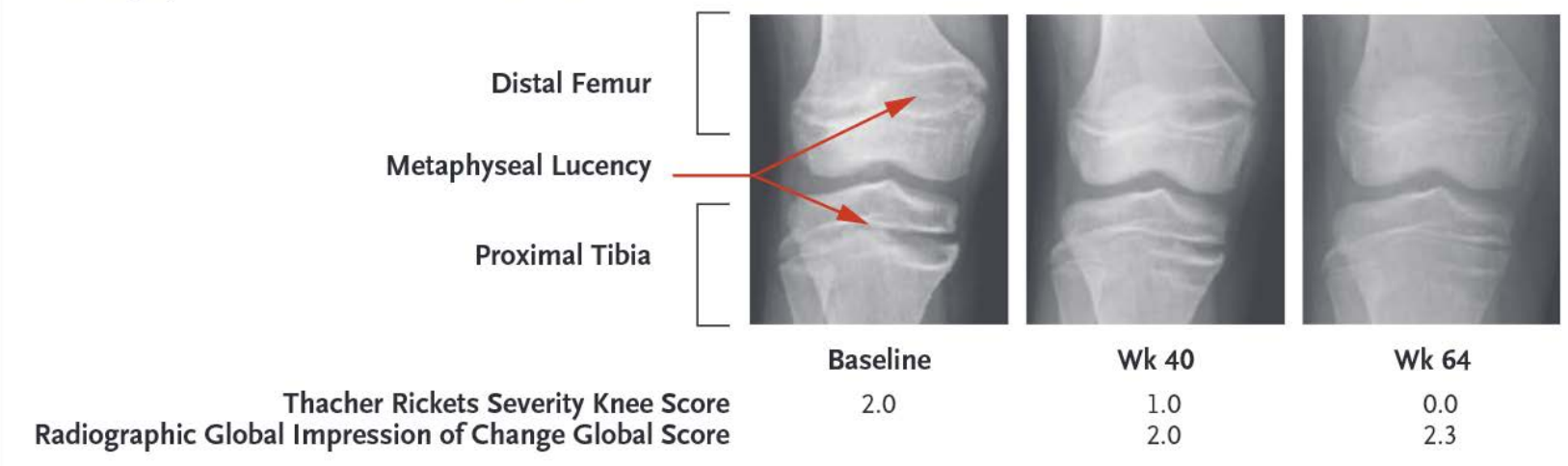
Maximized Subject History to Evaluate Individual Treatment Response

- Comprehensive medical/surgical history data from trial subjects taken to put burosumab response into context
 - Subjects with history of fractures had more pain and impairment at screening
- X-rays from pediatric trial subjects collected for up to 3 years prior to study enrollment to evaluate bone health with conventional therapy
- All available growth data for pediatric subjects collected to evaluate growth velocity prior to enrollment and allow for comparison to post-treatment period
 - Growth velocity z-scores may be more useful for evaluation of growth in shorter duration trials

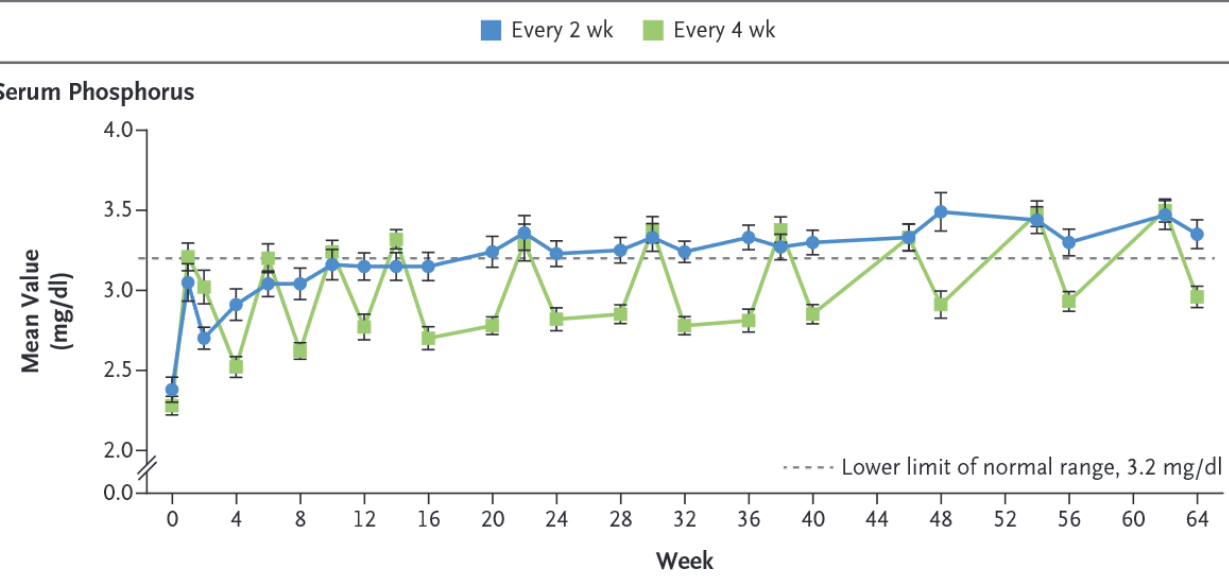
Modified Trial Based on Preliminary Analysis

- Preliminary data from first cohort of children evaluated to ensure adequacy of trial design
- Original protocol allowed for enrollment of subjects with rickets and/or bowing deformity
- 40-week results suggested near complete healing of rickets in those with rachitic disease at screening
- Protocol amended and expanded to enrich study population for RSS, the primary endpoint in the study
- Results from 40 weeks of treatment for full cohort suggest superiority of Q2 to Q4 dosing regimen leading all subjects to be transitioned to Q2
 - Week 40 data from first 36/52 subjects submitted in BTD application

C Radiographs of the Knee in an 11-Year-Old Girl



A Serum Phosphorus



Reference: Carpenter TO et al.
Burosumab Therapy in Children
with X-Linked Hypophosphatemia.
N Engl J Med 2018;378;21

Validated PROs to Evaluate Disease Burden and Treatment Response

- PROs selected based on feedback received from those with XLH
- Qualitative interviews, including concept elicitation and cognitive debriefing, performed with pediatric caregivers and affected adults
- Validation performed to confirm appropriateness of measures and support clinical meaningfulness of results in accordance with FDA Guidance
 - POSNA PODCI/PROMIS for children and BPI/WOMAC for adults
- Improvement in rickets severity scores supported by improvements in 6MWT and POSNA PODCI
- Changes in serum phosphorus and fracture healing supported by improvements in BPI-Q3 and WOMAC Stiffness/Physical Function

Monitor Long-Term Disease and Treatment Outcomes in a Real-World Setting

- Disease Monitoring Program initiated to monitor outcomes in up to 500 children and adults living with XLH for 10 years
- Long-term safety and efficacy of burosumab for clinical trial subjects, as well as those transitioning to burosumab post-approval, will be evaluated through this program
- Outcomes in patients not treated with burosumab will also be followed
- Up to 35 sites to be initiated in US, Canada and Latin America
- Program provides more insight into disease progression and treatment outcomes than traditional long-term extension studies

Summary

- Survey studies and endpoint development should begin prior to IND filing to optimize the design of first clinical trial
- Disease-specific endpoints can be critical for the interpretation of clinical efficacy response in a small study
- Leveraging historical data, selecting objective endpoints and utilizing rigorous rating techniques should be considered when a placebo arm is not feasible
- Conducting early “learn” studies that allow for adjustments to maximize use of subject data can accelerate development
- Investing in a comprehensive, robust and strategic program to evaluate long-term outcomes can help answer questions that can’t be studied in a clinical trial

Conclusion

- The clinical development and subsequent approval of burosumab is an example of a successful collaboration between industry and FDA that accelerated a rare disease program
- A dedicated COE group with rare disease experience could facilitate the early implementation of strategies, such as those used in the burosumab program, to improve the model for rare disease drug development

References

- Burosumab Therapy in Children with X-Linked Hypophosphatemia. Carpenter TO, Whyte MP, et al. N Engl J Med. 2018 May 24;378(21):1987-1998.
- A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial Evaluating the Efficacy of Burosumab, an Anti-FGF23 Antibody, in Adults With X-Linked Hypophosphatemia: Week 24 Primary Analysis. Insogna KL, Briot K, et al. JBMR. 2018 June 26;33(8):1383-1393.
- Qualitative Research to Explore the Patient Experience of X-linked Hypophosphatemia and Evaluate the Suitability of the BPI and WOMAC as Clinical Trial Endpoints. Theodore-Oklotu C, Bonner N, et al. Value Health. 2018 Aug;21(8):973-983.