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Assessment of Pain, Stiffness, and Physical Functioning Pre and During Burosumab Among Adults With X-linked Hypophosphatemia: Results from a Multinational, Long-term, Prospective Outcomes Disease Monitoring Program

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BACKGROUND

- In X-linked hypophosphatemia (XLH), excess FGF23 causes hypophosphatemia, leading to chronic debilitating musculoskeletal impairments[1]
- Treatment options for patients with XLH include the combination of oral phosphate and active vitamin D, or burosumab, a fully-human monoclonal antibody to FGF23 approved to treat patients 6 months of age and older with XLH[1,2]
- XLH symptoms include bone and joint pain, stiffness, and fatigue[1,2]
- Adults with XLH experience progressively debilitating complications that significantly impact functional independence and quality of life, including the ability to work[3,4]

OBJECTIVES

- Previous research validated the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in adults with XLH[5,6]
- This study assessed the impact of burosumab administration on WOMAC among adults from an XLH Disease Monitoring Program (DMP; ClinicalTrials.gov Identifier: NCT03651505)

METHODS

Database: The XLH-DMP

- The XLH-DMP is a global, prospective, multicenter, longitudinal, long-term outcomes program for patients receiving or not receiving any treatment for XLH that is designed to:
  - Characterize XLH disease presentation and progression
  - Assess long-term safety and effectiveness of burosumab
  - Prospectively investigate longitudinal changes over time across biomarkers, clinical assessments, and patient/caregiver-reported outcome measures in a representative population
- The XLH-DMP is collecting demographic, biochemical, physiologic, disease severity, and disease progression data in patients taking burosumab and those not taking burosumab
- Patients only have access to burosumab through authorized prescribed use

XLH-DMP Eligibility

- Inclusion Criteria:
  - Willing and able to provide informed consent or, in the case of patients under the age of 18 years (or 16 years, depending on the region), provide assent (if required) and informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures
  - Clinical diagnosis of XLH based on family history, or confirmed PHEX mutation, or biochemical profile consistent with XLH
  - Willing and able to comply with the study visit schedule and study procedures
- Exclusion Criteria:
  - Concurrent enrollment in an Ultragenyx-sponsored clinical trial
  - Serious medical or psychiatric comorbidity
  - Less than one year of life expectancy

Patient Selection for This Analysis

- XLH patients in the DMP as of February 2022, age ≥ 18 years at DMP enrollment, without history of burosumab (burosumab-naïve)
- Only US and Canada patients with complete information on WOMAC domains at baseline and one-year post-baseline were included and grouped into three cohorts:
  1. Burosumab-naïve at enrollment with burosumab dosed within 90 days post-enrollment
  2. Burosumab-naïve at enrollment with burosumab dosed between 91–180 days post-enrollment
  3. No-burosumab history at baseline or within one year of enrollment

Study Outcomes

- The WOMAC has 24 items across three subscales: Pain (5 items), stiffness (2 items), and physical function (17 items)
- WOMAC scores collected from adults at enrollment were compared with scores obtained one year later for each of the three cohorts by subscale

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RESULTS

Table 1. XLH-DMP Baseline Patient Characteristics

Characteristic	Cohort 1: burosumab dosed within 90 days post-enrollment N = 24	Cohort 2: burosumab dosed from 91 to 180 days post-enrollment N = 14	Cohort 3: no burosumab at baseline or within one year of enrollment N = 51
Age			
Mean (SD)	39.2 (14.8)	41.9 (14.6)	43.4 (15.6)
Median	38.2	40.8	44
Min, Max	18.6, 66.0	20.6, 66.8	18.2, 76.9
Q1, Q3	26.6, 50.2	32.6, 53.2	31.5, 53.0
Pooled Age Groups, n (%)			
< 65 Years	23 (96)	13 (93)	45 (88)
≥ 65 Years	1 (4.2)	1 (7.1)	6 (12)
Sex, n (%)			
Female	18 (75)	12 (86)	44 (86)
Male	6 (25)	2 (14)	7 (14)
Ethnicity, n (%)			
Hispanic or Latino	0 (0)	2 (14)	7 (14)
Not Hispanic or Latino	23 (96)	8 (57)	35 (69)
Not Reported	1 (4)	4 (29)	9 (18)
Unknown	0 (0)	0 (0)	0 (0)
Race, n (%)			
Black or African American	2 (8)	0 (0)	1 (2.0)
Not Reported	1 (4)	4 (29)	9 (18)
Other	0 (0)	0 (0)	0 (0)
Unknown	0 (0)	0 (0)	0 (0)
White	21 (88)	10 (71)	41 (80)
Country, n (%)			
Canada	1 (4)	4 (29)	11 (22)
United States	23 (96)	10 (71)	40 (78)
Body Mass Index			
n	23	14	46
Mean (SD)	32.9 (9.9)	30.419 (7.33)	30.9 (8.71)
Median	31.5	28.9	29.3
Min, Max	19.7, 67.6	23.1, 49.0	18.8, 62.5
Q1, Q3	26.2, 33.8	26.1, 30.8	24.8, 34.0
Serum Phosphorus (mg/dL)			
n	24	14	51
Mean (SD)	2.16 (0.47)	2.32 (0.25)	2.25 (0.46)
Median	2.1	2.2	2.2
Min, Max	1.4, 3.3	2.0, 2.9	1.6, 4.1
Q1, Q3	1.9, 2.4	2.2, 2.5	1.9, 2.4

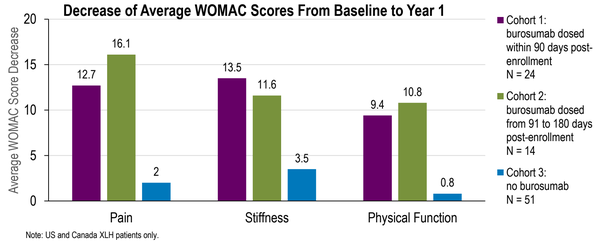
- As of February 2022, 24 and 14 burosumab-naïve and 51 no-burosumab patients from North America were in cohorts 1, 2, and 3
- The average age was 39.2, 41.9 and 43.4 across the three cohorts, respectively
- A majority of patients were < 65 years old, female, white, and were enrolled in the United States across all three cohorts
- Baseline body mass index and was 32.9, 30.4, 30.9 across the three cohorts, respectively
- Serum phosphorus levels were similar across cohorts at baseline

Table 2. Summary Descriptive Results for WOMAC Subscales at XLH-DMP Baseline and Year 1

	XLH-DMP Baseline			Year 1		
	Cohort 1: burosumab dosed within 90 days post-enrollment N = 24	Cohort 2: burosumab dosed from 91 to 180 days post-enrollment N = 14	Cohort 3: no burosumab at baseline or within one year of enrollment N = 51	Cohort 1: burosumab dosed within 90 days post-enrollment N = 24	Cohort 2: burosumab dosed from 91 to 180 days post-enrollment N = 14	Cohort 3: no burosumab at baseline or within one year of enrollment N = 51
WOMAC Pain Score						
Mean (SD)	35.6 (19.96)	43.2 (23.75)	24.8 (20.15)	22.9 (20.69)	27.1 (26.51)	22.8 (20.67)
Median	35	42.5	20	20	17.5	20
Min, Max	0.0, 70.0	5.0, 100.0	0.0, 70.0	0.0, 75.0	0.0, 100.0	0.0, 85.0
Q1, Q3	25.0, 46.2	30.0, 53.8	10.0, 44.4	7.5, 35.0	10.0, 35.0	5.0, 35.0
WOMAC Stiffness Score						
Mean (SD)	51.0 (18.4)	51.8 (20.72)	34.1 (24.12)	37.5 (20.85)	40.2 (19.72)	30.6 (23.36)
Median	50	50	25	37.5	37.5	25
Min, Max	25.0, 87.5	25.0, 100.0	0.0, 87.5	0.0, 87.5	12.5, 87.5	0.0, 100.0
Q1, Q3	37.5, 62.5	37.5, 62.5	25.0, 50.0	25.0, 50.0	25.0, 50.0	12.5, 43.8
WOMAC Physical Function Score						
Mean (SD)	32.8 (22.34)	39.0 (26.13)	19.3 (19.57)	23.4 (22.2)	28.2 (24.61)	18.5 (19.93)
Median	35.3	41.2	13.2	17.6	22.8	16.2
Min, Max	1.5, 70.6	0.0, 100.0	0.0, 69.1	0.0, 73.5	0.0, 97.1	0.0, 85.3
Q1, Q3	11.4, 49.6	23.5, 51.5	1.5, 32.4	4.4, 37.1	16.5, 39.7	1.5, 27.9

- At Year 1, Cohort 1 patients were treated with burosumab for least 270 days and Cohort 2 patients were treated for at least 180 days
- At baseline, mean WOMAC scores were 35.6, 51.0, 32.8 for pain, stiffness, and physical function for Cohort 1, 43.2, 51.8, 39.0 for Cohort 2, and 24.8, 34.1, 19.3 for Cohort 3

Figure 1. Improvement in Average WOMAC Scores From XLH-DMP Baseline to Year 1 by Cohort



Note: US and Canada XLH patients only.

- Minimum clinically important differences for the WOMAC[7] are:
  - Pain: 9.7
  - Stiffness: 10
  - Physical Function: 9.3
- Clinical meaningful WOMAC improvements were observed in all domains among burosumab-treated cohorts while the no-burosumab cohort had minimal changes
- The effect of burosumab, relative to placebo, on WOMAC pain, stiffness and physical function was also evident by Week 12 in a phase 3 (UX023-CL303) burosumab trial[8]
- The baseline average WOMAC values for the no burosumab patients were lower compared with burosumab naïve patients at baseline and those treated within 180 days post-baseline
- Average score for all subscales and all cohorts decreased (improved) at Year 1 versus baseline

LIMITATIONS

- Real-world evidence is not standardized; there can be significant variance across cohorts
- Since WOMAC scores are patient-reported, they may be subject to recall bias and complicated by other treatment options *(eg*, surgery) or activities that might have impacted patient quality of life
- Results were summarized to indicate trends across different groups of patients and were not controlled for differences in baseline characteristics or statistically powered to detect difference between groups
- Limited sample sizes for study cohorts and study outcomes of interest could bias results

CONCLUSIONS

- Adult patients with XLH treated with burosumab for at least 180 days (and up to 360 days) reported improved quality of life in terms of pain, stiffness, and physical function as assessed using the WOMAC
  - Clinically meaningful improvements in stiffness, pain, and physical function were observed one year after XLH-DMP enrollment among adults with XLH receiving burosumab
- Improvements in WOMAC scores in this analysis were consistent with improvements in WOMAC scores reported in a randomized, double-blind, placebo-controlled registrational trial in adults with XLH[8]

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