Development of a Composite Endpoint in Hypophosphatasia in adults to Optimize Cost-Effectiveness Demonstration

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INTRODUCTION

- **Hypophosphatasia (HPP)** in adults is a **multisystem disease** characterized by **impaired mobility, chronic pain, fatigue, and reduced quality of life.** There is **no disease-specific scale available in HPP** for use in clinical studies. In this context, **treatment effect cannot be fully captured by a single endpoint.**
- **Traditional endpoints** (e.g., 6MWT) reflect functional capacity and endurance, but **fail to capture patient experience, symptom burden and quality of life.**
- Combining **objective performance measures** and **patient-reported outcome measures from the selected domains align with core aspects of HPP burden** (i.e., mobility/function, pain, fatigue, quality of life) ensures a **holistic and clinically meaningful assessment** of disease impact and treatment benefits.

OBJECTIVES

- Using Hickory trial data[1], assessing adults and adolescents with HPP, **develop a multidimensional composite endpoint** in adults with HPP integrating **functional outcomes** and **patient-reported outcomes,** to better capture disease burden and treatment effect, using **rescaling and aggregation methods.**
- Identify preferred **combination of instruments** , overall and by HPP onset
- Validate composite endpoints using **clinical anchors.**

CONCLUSIONS

- Composite endpoints demonstrated **strong convergent validity**, **longitudinal responsiveness**, and **good discrimination across severity groups**.
- **Multidomain composites** consistently outperformed simpler combinations, supporting integration of functional, pain, fatigue, and quality-of-life measures.
- The most comprehensive composite (**LEFS + FACIT-Fatigue + BPI-Pain + SF-36 + 6MWT + STS**) achieved the **best overall performance** across validation metrics.
- Findings support the use of a **multidimensional composite endpoint** to better capture disease burden and optimize assessment of treatment benefit in HPP.

Abbreviations
HPP: Hypophosphatasia; **PROMs**: Patient-Reported Outcome Measures; **LEFS**: Lower Extremity Functional Scale; **6MWT**: 6-Minute Walk Test; **STS**: Sit-to-Stand Test; **BPI-SF**: Brief Pain Inventory – Short Form; **FACIT-Fatigue**: Functional Assessment of Chronic Illness Therapy – Fatigue; **SF-36**: 36-Item Short Form Health Survey; **PCS**: Physical Component Summary; **MCS**: Mental Component Summary; **EQ-5D-5L**: EuroQol 5-Dimension 5-Level Questionnaire; **W25**: Week 25; **r**: Correlation coefficient.

METHODS

Step 1. Select instruments from four domains[2]

Domain	Patient-reported	Performance-based/ Functional
Physical function and mobility	LEFS Total Score	6MWT-Distance at 6 Minutes (m) Number of Times Participant Stands
Pain / symptom burden	BPI-SF Pain Severity Score	
Fatigue / energy	FACIT-Fatigue Total Score	
Health-related quality of life /emotional/ social participation	SF-36 - PCS Norm-Based Score SF-36 - MCS Norm-Based Score	

Step 2. Build composite endpoint[2]

Rescaling
Z-score standardization

Weighting
Equal weight (EW), i.e., assuming same importance of all sub-dimensions

Aggregation
Additive aggregation (poor outcomes can be counterbalanced by better outcomes),

Step 3. Validate composite endpoint

Clinical anchor selection
Use independent, clinically interpretable anchors (not included in composite) in key domains:
Mobility/function: ***EQ-5D-5L Mobility***
Pain: ***EQ-5D-5L Pain/Discomfort***

Convergent validity
Assess correlation between composite and clinical anchors

Longitudinal validity
Assess correlation of changes baseline/W25, Δcomposite vs Δanchor

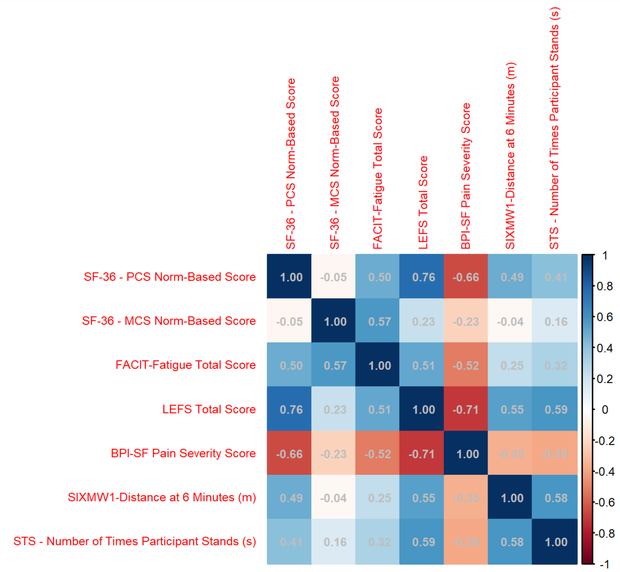
Known-groups validity
Compare composite across anchor categories

Kappa agreement[3]
Ability to correctly categorize patients with anchors

Rankings and selection of composite
Composite validity, overall and by disease onset

RESULTS AND INTERPRETATION

Relationships between selected instruments



- Overall, **low to moderate correlations between instruments support the development of composite endpoint**.
- BPI-SF pain severity showed moderate-to-strong negative correlations with function and fatigue outcomes (r=-0.52 to -0.71).
- **Objective performance tests (6MWT, STS) moderately correlated with patient-reported function** (LEFS: r=0.55–0.59)**, supporting a composite endpoint approach.**

Composite endpoints tested were validated and ranked

Instrument combinations All adults, n=96 Adults with adult onset, n=53 Adults with pediatric onset, n=43	Rankings (1 indicated the best ranking)																	
	Convergent validity						Longitudinal validity						Kappa statistics					
	EQ-5D-5L Mobility			EQ-5D-5L Pain/Discomfort			EQ-5D-5L Mobility			EQ-5D-5L Pain/Discomfort			EQ-5D-5L Mobility			EQ-5D-5L Pain/Discomfort		
	All adults	Adu. onset	Ped. onset	All adults	Adu. onset	Ped. onset	All adults	Adu. onset	Ped. onset	All adults	Adu. onset	Ped. onset	All adults	Adu. onset	Ped. onset	All adults	Adu. onset	Ped. onset
FACIT-Fatigue + BPI-Pain	11	11	11	9	10	5	11	11	11	7	6	11	4	7	2	6	4	6
6MWT + BPI-Pain	7	5	8	8	6	10	10	9	9	10	10	9	8	8	6	7	6	8
SF-36 + FACIT-Fatigue + BPI-Pain	10	10	10	11	11	3	8	10	7	4	3	6	1	3	1	2	2	3
6MWT + BPI-Pain + STS	4	3	7	10	4	11	9	7	10	11	11	7	11	11	11	9	11	7
6MWT + BPI-Pain + FACIT-Fatigue	9	8	9	6	8	8	7	8	6	9	8	10	9	9	9	10	7	10
6MWT + BPI-Pain + SF-36	3	4	3	3	2	2	2	3	3	2	2	1	2	1	3	1	1	1
6MWT + BPI-pain + STS + FACIT-Fatigue	6	6	5	5	5	9	6	5	8	8	9	8	10	10	10	11	8	11
6MWT + BPI-Pain + STS + SF-36	2	2	2	2	1	4	5	2	5	3	5	2	5	5	4	4	9	2
6MWT + BPI-Pain + FACIT-Fatigue + SF-36	8	9	6	7	9	6	4	6	2	5	4	5	3	2	5	5	5	4
6MWT + BPI-pain + STS + FACIT-Fatigue + SF-36	5	7	4	4	7	7	3	4	4	6	7	4	6	6	7	8	10	9
LEFS + FACIT-Fatigue + BPI-Pain + SF-36 + 6MWT + STS	1	1	1	1	3	1	1	1	1	1	1	3	7	4	8	3	3	5

- The most comprehensive composite (**LEFS + FACIT-Fatigue + BPI-Pain + SF-36 + 6MWT + STS**) achieved the best overall validity rankings, supporting multidimensional assessment of function, pain, fatigue, and mobility. (know-groups validity was excellent for all combinations)
  Among simplified composites, **SF-36 + FACIT-Fatigue + BPI-Pain**, **6MWT + BPI-Pain + STS + SF-36**, and **6MWT + BPI-Pain + SF-36** showed balanced and consistently favorable rankings across validity and agreement metrics in both adult and pediatric onset groups, representing strong alternatives to the full multidomain composite.

References

1. ClinicalTrials.gov. Phase 3 study of ALXN1850 versus placebo in adolescent and adult participants with HPP who have not previously been treated with asfotase alfa (HICKORY). NCT Identifier: NCT06079281. Available at https://clinicaltrials.gov/study/NCT06079281.
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3. McHugh, M. L. (2012). Interrater reliability: The kappa statistic. *Biochemia Medica*, *22*(3), 276–282.