WITH HYPOPHOSPHATASIA

A COMPROMISED FOUNDATION IS A COMPROMISED FUTURE[1-3]

ALEXION®

ASSESS. ASK. ACT.

The patients presented on this page are hypothetical patients

Hypophosphatasia (HPP) is a progressive, systemic, inherited metabolic disorder[1,4,5]

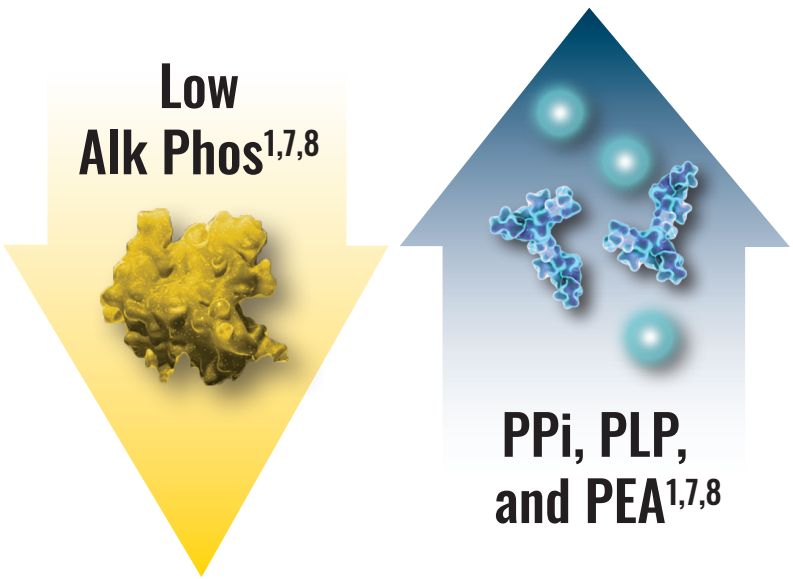
In HPP, a loss-of-function mutation in the *ALPL* gene leads to deficient alkaline phosphatase (Alk Phos) enzyme activity, the biochemical hallmark of HPP[1,6]

In healthy bone

- Alk Phos activity results in the generation of hydroxyapatite and bone mineralization[1,6]

In HPP, low Alk Phos activity

- Leads to substrate (PPi, PLP, PEA) accumulation that results in[1,5,7]
  - Impaired bone mineralization leading to diminished bone strength and quality
  - Multisystemic complications
- May impact calcium and phosphate regulation[1]



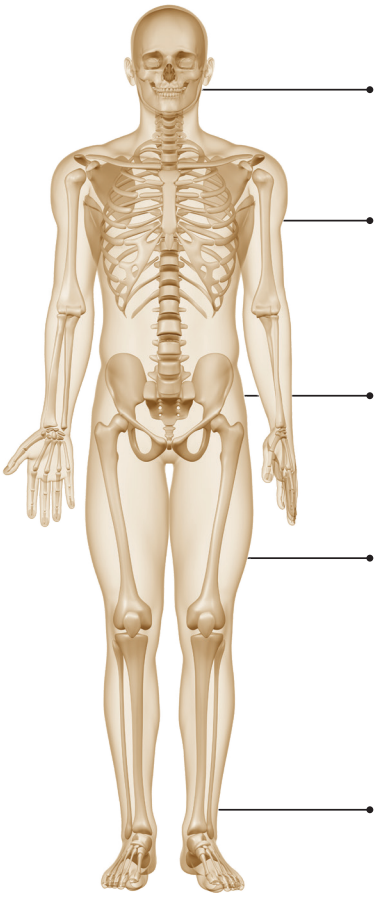
Alk Phos, alkaline phosphatase; HPP, hypophosphatasia; PEA, phosphoethanolamine; PLP, pyridoxal 5'-phosphate; PPi, inorganic pyrophosphate.

Patients with HPP may experience unpredictable, devastating, and life-limiting consequences[1,5]

HPP is a heterogeneous disease[1,4,9]

- Age at presentation and severity of symptoms vary broadly[1,4,9]

Systemic Manifestations of HPP



- Premature primary tooth loss with the root intact[1,5,10,11]
- Abnormal dentition[1]
- Periodontal disease[12,13]

- HPP-related rickets/osteomalacia[14,15]
- Skeletal deformities[1,5]
- Bone pain[5]
- Fractures[1,5,16-18]

Hypercalcemia/hypercalciuria leading to[1,5,19-22]

- Nephrocalcinosis
- Renal damage

- Muscle/joint pain[1,5]
- Muscle weakness[1,5,23]
- CPPD/pseudogout/chondrocalcinosis[1]
- Unusual gait[1,5,23]
- Impaired mobility/ambulation[5]
- Fatigue[2,5]

- Short stature[1,5]
- Failure to thrive[1,5]
- Developmental delays[15,24]
- Missed motor milestones[1,5,15]

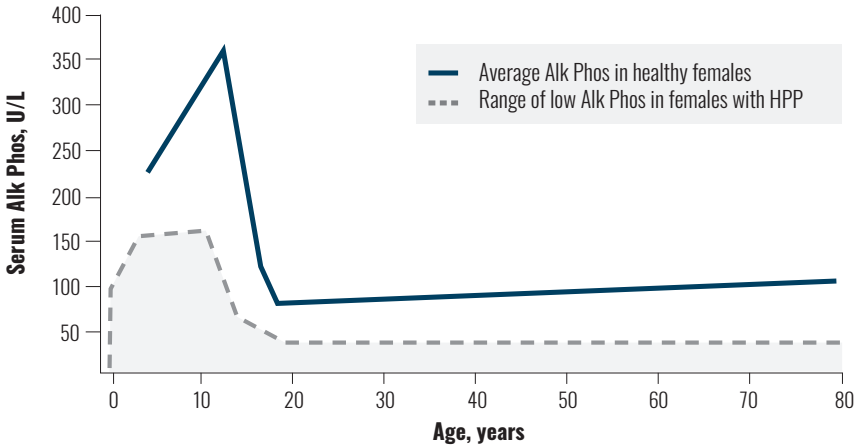
Because HPP is rare and the presentation can vary, it may be mistaken for other skeletal, rheumatologic, and metabolic disorders[1,5,25]

- HPP is diagnosed based on the presence of one or more key clinical signs/symptoms with low Alk Phos activity[5]

CPPD, calcium pyrophosphate deposition.

In HPP, Alk Phos activity levels are low throughout life[8]

Average Alk Phos in healthy females vs Range of Alk Phos levels that may be indicative of HPP in females[1,26-29,a,b]



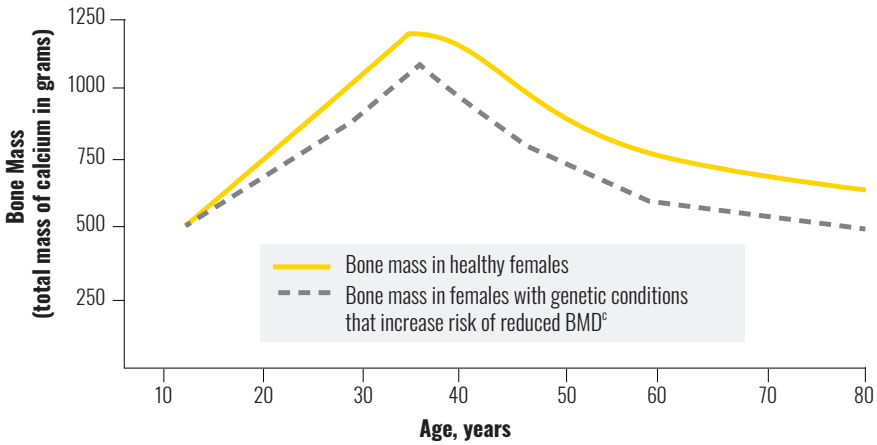
Alk Phos levels are highest during childhood, years before peak bone mass is achieved[26]

U/L, units per liter.

[a]Based on data and reference intervals from the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) project (Colantonio et al. 2012). Caliper values used were from healthy females aged 3 to 79, from 2007 to 2011.[1,26-29] [b]Sample graph of Alk Phos values for females from CALIPER, Adeli 2015, and Schumann 2011. Values for normal Alk Phos may vary by lab and must be adjusted for age and sex.[27,28]

Reduced levels of Alk Phos during bone mass development in childhood may impact peak bone mass in adulthood[26,30]

Peak bone mass in healthy females vs Females with factors or diseases that increase the risk of osteopenia/osteoporosis and fracture later in life[31]



In adulthood, mineralization deficits can lead to risk of osteopenia, osteoporosis, and increased risk of fracture[31]

BMD, bone mineral density.

[c]Curve is a representative line of peak bone mass seen in females with conditions or factors that influence peak bone mass, including chronic diseases, endocrine factors and diseases, auxological features, genetic factors, and pharmacological treatments.[31]

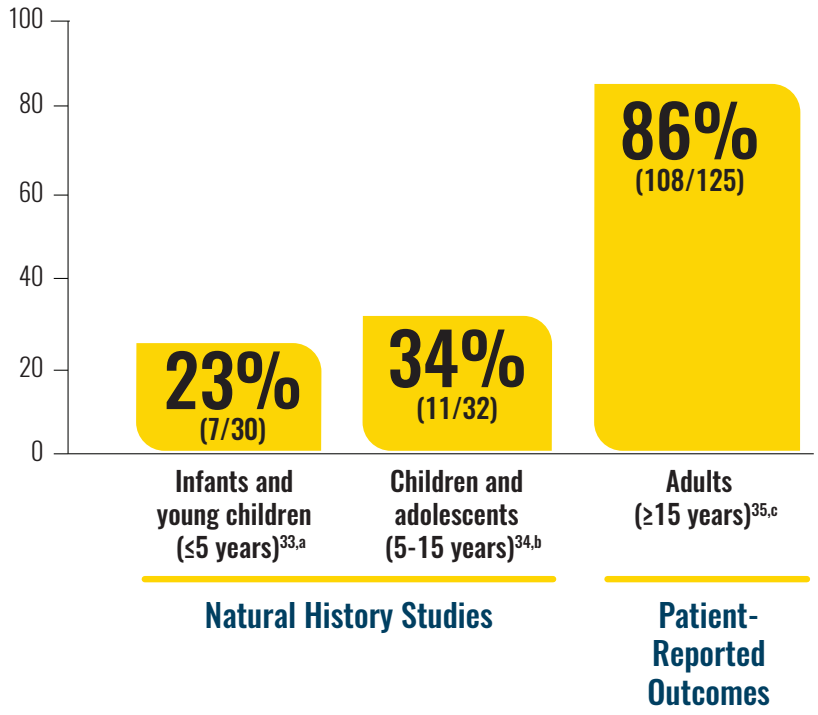
Low Alk Phos and impaired bone quality during growth years can be a risk factor for long-term consequences[1,31]

Disease Burden in HPP[3]

- Developmental delays[15,24]
- Unusual gait[5,23]
- Impaired mobility[5]
- Fractures[1,5]
- Bone, muscle, or joint pain[1,5]
- Fatigue[2,5]
- Missed school or work[21,32]
- Limited ability to perform everyday activities[3]
- Decreased quality of life[3]

Over the course of a lifetime, patients with HPP can experience accumulated burden of disease[3]

Percentage of patients with HPP with fractures[33-35]

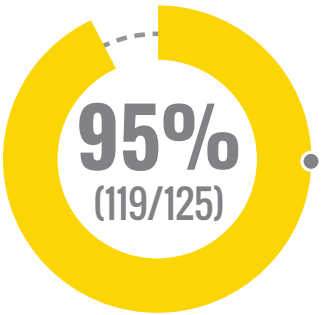


On average, patients with HPP experience **13 fractures** during their lifetime[35]

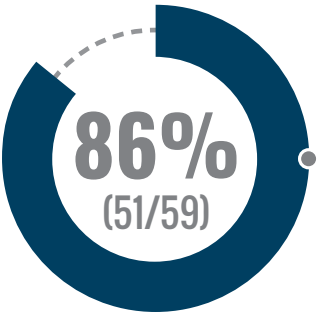
[a]Data from a noninterventional, retrospective chart review study designed to understand the natural history of 48 patients ≤5 years of age with severe perinatal- and infantile-onset HPP. Patients included in the study were those diagnosed with HPP based on at least one of the following: serum biomarker levels (below-normal Alk Phos and above-normal PLP or PEA), below-normal Alk Phos and radiographic abnormalities, or genetic analysis of the *ALPL* gene. Additionally, onset of HPP must have occurred prior to 6 months of age based on signs that included at least one of the following: respiratory compromise, rachitic chest deformity, and/or vitamin B_6–responsive seizures.[33] [b]Data from a retrospective, multinational, noninterventional natural history study of childhood HPP in patients 5 to 15 years of age (N=32).[34] [c]Combined data from HIPS/HOST, an Internet questionnaire and telephone survey that queried demographics, HPP-related illness history, disease progression, and health-related quality of life. One hundred twenty-five adults participated.[35]

"The biggest struggle for me is the energy, and keeping my pain at a place where I can still function." - Brittan, patient with HPP

In a survey conducted in patients with HPP[3,36,d]



of adults with HPP reported HPP-related pain[3,e]



of children and adolescents with HPP experienced pain[36]

HPP can cause a high burden of illness with a risk of accumulation or worsening of symptoms over time[2,3,20,37,38]

[d]Combined data from HIPS/HOST, an Internet questionnaire and telephone survey that queried demographics, HPP-related illness history, disease progression, and health-related quality of life. One hundred twenty-five adults and fifty-nine children participated.[3,36] [e]76% of the adult patients in the HIPS survey (n=84) stated that their bone pain was severe enough to limit activity.[3]

Early diagnosis of HPP is critical[1,39]

ANY SIGN/SYMPTOM IN ONE OF THESE SYSTEMS[1,5]

DENTAL[3,5,40]

GROWTH/ DEVELOPMENT[1,5]

MUSCULAR STRENGTH/ FUNCTION[5,23]

SKELETAL[3,5,34]

RENAL[1,5]

+

LOW AGE- AND SEX-ADJUSTED ALK PHOS ACTIVITY[1,5,25]

=

HPP DIAGNOSIS[1,5,25]

When considering a diagnosis of HPP, rule out secondary causes of low Alk Phos, including[5,40,a]

- Certain medications
- Large blood transfusions
- Improper blood collection
- Profound hypothyroidism
- Celiac disease
- Severe malnutrition
- Pernicious anemia
- Wilson disease
- Multiple myeloma
- Magnesium, vitamin C, or zinc deficiency

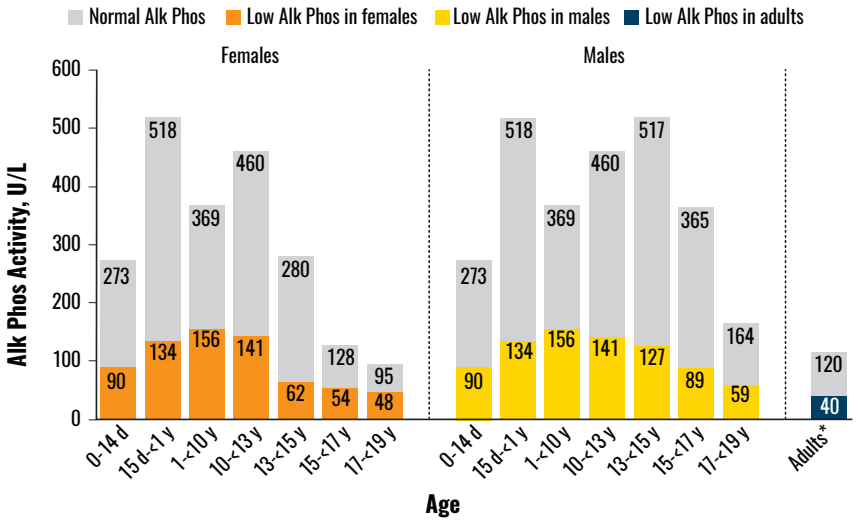
NOTE: The information in this presentation is intended as educational information for healthcare professionals. It does not replace a healthcare professional's judgment or clinical diagnosis.

[a]Not an all-inclusive list.

Age- and sex-adjusted Alk Phos reference intervals must be used to correctly diagnose HPP[1]

Low Alk Phos may not be flagged if your laboratory does not use age- and sex-adjusted reference intervals in children when testing Alk Phos activity[1,27]

Age- and sex-adjusted Alk Phos reference ranges, U/L[27-29]



When you suspect HPP, review your lab results critically, as some labs might not use age- and sex-adjusted reference intervals for Alk Phos[1,27]

*The age- and sex-adjusted Alk Phos reference range provided is approximate. Alk Phos reference ranges vary based upon lab. Refer to your lab for the appropriate reference range.

d, day; y, year.

NOTE: Graph adapted from the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) project (Colantonio et al. 2012). Caliper samples from 1072 male and 1116 female participants (newborn to 18 years) were used to calculate age- and sex-specific reference intervals. No variation in Alk Phos based on ethnic differences was observed. Reference intervals shown were established on the Abbott ARCHITECT c8000 analyzer.

Misdiagnosis and delayed diagnosis can lead to ineffective management[1]

Patients with HPP may be misdiagnosed with other, more common conditions[1,19,25,42-48]

Misdiagnosis	Treatment	Impact on Patients With HPP
Osteoporosis/ Osteopenia	Bisphosphonates[1,25,42-44]	Analogues to PPi; may worsen skeletal hypomineralization in HPP
	Hormone therapy[44-46]	Does not address the underlying cause of HPP
	RANKL inhibitor[47]	Does not address the underlying cause of HPP
Rickets/ Osteomalacia	High-dose vitamin D and calcium[1,19]	Can exacerbate hypercalcemia and hypercalciuria in HPP
Fibromyalgia	GABA analogues[48]	Does not address the underlying cause of HPP

Rule out HPP before initiating any of these treatments[1]

GABA, gamma-aminobutyric acid; RANKL, receptor activator of nuclear factor kappa-ß ligand.

Additional assessments can inform diagnosis and management of HPP[49]

Vitamin B_6 (PLP)

- PLP is a substrate of Alk Phos, and levels are often elevated in patients with HPP but may be borderline or within normal range[39,41,50,51]

Genetic testing

- Detection of an *ALPL* mutation can support diagnosis when biochemical and clinical data are not clear[49]
  - Prediction of a phenotype from a genotype may be unreliable[4]
- Lack of an identified *ALPL* gene mutation or report of a variant of unknown significance cannot be used to exclude a diagnosis of HPP[49,a]

Physical therapy

- Physical therapy can serve an important role in the functional evaluation and ongoing management of a patient with HPP[49]

Performing these assessments may help with diagnosing and managing your patients with HPP[49]

[a]Standard sequencing of *ALPL* by Sanger or next-generation sequencing may miss approximately 5% of known *ALPL* mutations.[49]

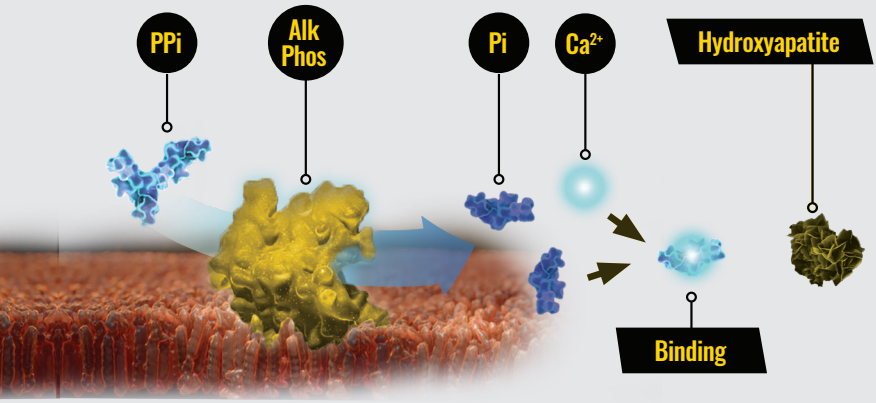
NOTE: The information in this presentation is intended as educational information for healthcare professionals. It does not replace a healthcare professional's judgment or clinical diagnosis.

Functional Alk Phos is essential for building strong, quality bone[1,6,52]

Bone strength is derived through formation and deposition of hydroxyapatite crystals[1,6,52]

The role of Alk Phos in healthy bone[1,6,52]

Alk Phos splits inorganic pyrophosphate (PPi), releasing inorganic phosphate (Pi) that binds with calcium (Ca^{2+}) to form hydroxyapatite—the building block of bone mineralization[6]



Figures created by Alexion Pharmaceuticals, Inc. for illustrative purposes

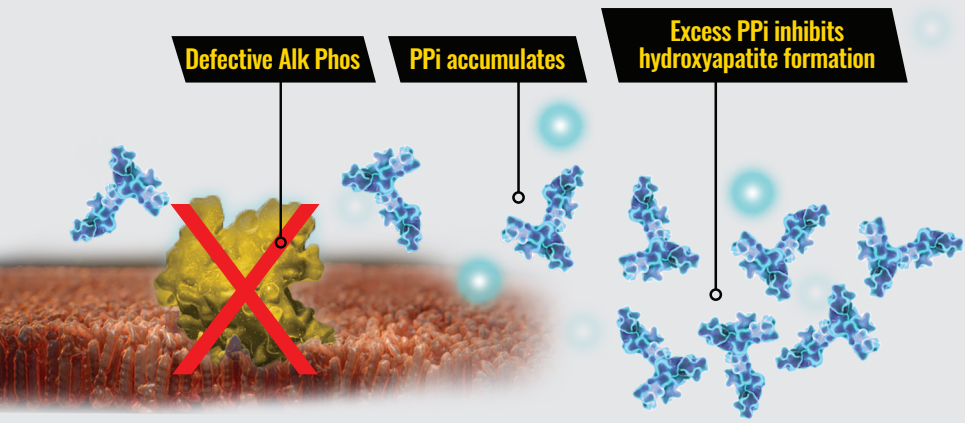
Hydroxyapatite is essential for mineralization and building functional strength in bone[6]

In HPP, a loss-of-function mutation in ALPL leads to low Alk Phos enzyme activity, impairing bone mineralization[1]

This enzymatic defect leads to accumulation of substrates and altered calcium and phosphate regulation, resulting in poor bone mineralization, diminished bone strength/quality, and multisystemic complications[1]

Bone in HPP[1]

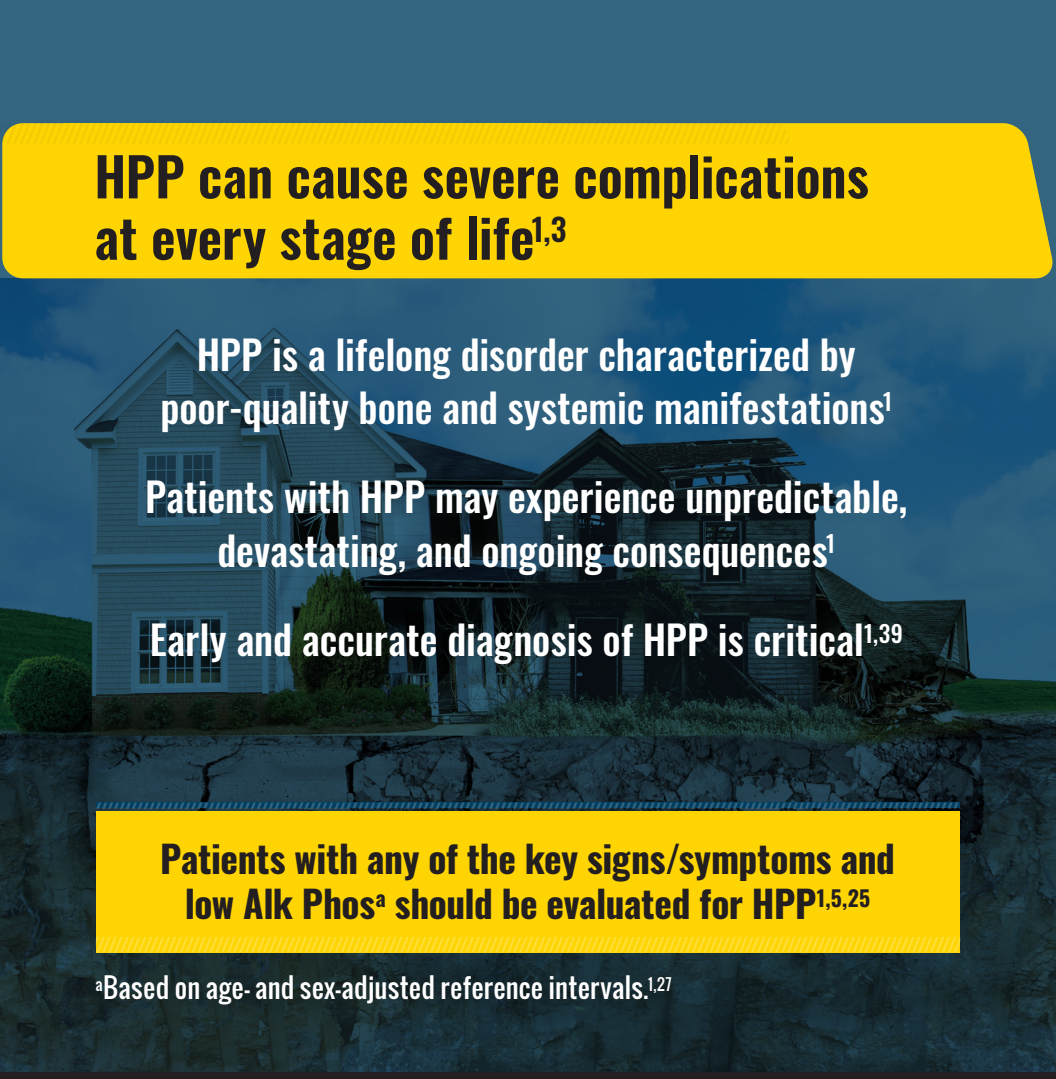
Impaired/low Alk Phos activity results in accumulation of PPi, a potent inhibitor of hydroxyapatite formation, leading to diminished bone mineralization[1]



Figures created by Alexion Pharmaceuticals, Inc. for illustrative purposes

Low Alk Phos activity results in disrupted bone mineralization that has physical and metabolic consequences throughout life[1]

HPP can cause severe complications at every stage of life[1,3]



HPP is a lifelong disorder characterized by poor-quality bone and systemic manifestations[1]

Patients with HPP may experience unpredictable, devastating, and ongoing consequences[1]

Early and accurate diagnosis of HPP is critical[1,39]

Patients with any of the key signs/symptoms and low Alk Phos[a] should be evaluated for HPP[1,5,25]

[a]Based on age- and sex-adjusted reference intervals.[1,27]

1. Rockman-Greenberg C. *Pediatr Endocrinol Rev.* 2013;10(suppl 2):380-388. **2.** Mori M, et al. *Bone Rep.* 2016;5:228-232. **3.** Weber TJ, et al. *Metabolism.* 2016;65(10):1522-1530. **4.** Mornet E. *Metabolism.* 2018;82:142-155. **5.** Bishop N, et al. *Arch Dis Child.* 2016;101(6):514-515. **6.** Orimo H. *J Nippon Med Sch.* 2010;77(1):4-12. **7.** Whyte MP, et al. *Bone.* 2017;102:15-25. **8.** Bianchi ML. *Osteoporos Int.* 2015;26(12):2743-2757. **9.** Whyte MP, et al. *Bone.* 2016;93:125-138. **10.** Reibel A, et al. *Orphanet J Rare Dis.* 2009;4:6. **11.** Whyte MP, et al. *Am J Med.* 1982;72(4):631-641. **12.** Foster BL, et al. *J Dent Res.* 2014;93(7):7S-19S. **13.** Watanabe H, et al. *J Periodontol.* 1993;64(3):174-180. **14.** Whyte MP, et al. *N Engl J Med.* 2012;366(10):904-913. **15.** Beck C, et al. *Rheumatol Int.* 2011;31(10):1315-1320. **16.** Coe JD, et al. *Bone Joint Surg Am.* 1986;68(7):981-990. **17.** Gagnon C, et al. *J Clin Endocrinol Metab.* 2010;95(3):1007-1012. **18.** Schalin-Jäntti C, et al. *J Clin Endocrinol Metab.* 2010;95(12):5174-5179. **19.** Mohn A, et al. *Acta Paediatr.* 2011;100(7):e43-e46. **20.** Whyte MP. London, UK: Academic Press; 2013:337-360. **21.** Eade AWT. *Ann Rheum Dis.* 1981;40(2):164-170. **22.** Whyte MP, et al. *Clin Endocrinol Metab.* 2013;98(12):4606-4612. **23.** Weber TJ, et al. Poster presented at: International Conference on Children's Bone Health; June 22-25, 2015; Rotterdam, Netherlands. **24.** Seshia SS, et al. *Arch Dis Child.* 1990;65(1):130-131. **25.** Mornet E, Nunes ME. *GeneReviews.* Seattle, WA: University of Washington, Seattle; 1993-2018. Updated February 4, 2016. Accessed February 14, 2018. **26.** Clarke J, et al. Understanding your health by using reference ranges. Statistics Canada website. http://www.statcan.gc.ca/pub/82-624-x/2016001/article/14637-eng.pdf. Accessed February 14, 2018. **27.** Colantonio DA, et al. *Clin Chem.* 2012;58(5):854-868. **28.** Adeli K, et al. *Clin Chem.* 2015;61(8):1049-1062. **29.** Schumann G, et al. *Clin Chem Lab Med.* 2011;49(9):1439–1446. **30.** Davies JH, et al. *Arch Dis Child.* 2005;90(4):373-378. **31.** Maggioli C, et al. *Ann Pediatr Endocrinol Metab.* 2017;22(1):1-5. **32.** Braunstein NA, et al. *Bone Rep.* 2015;4:1-4. **33.** Whyte MP, et al. Poster presented at: 2014 Pediatric Academic Societies and Asian Society for Pediatric Research Joint Meeting; May 3-6, 2014; Vancouver, BC. **34.** Whyte MP, et al. LB-OR01-4. Endocrine Society's 97th Annual Meeting and Expo website. https://endo.confex. com/endo/2015endo/webprogram/Paper22822.html. Accessed February 14, 2018. **35.** Weber TJ, et al. Poster presented at: Endocrine Society Annual Meeting; March 5-8, 2015; San Diego, CA. **36.** Data on file. Boston, MA: Alexion Pharmaceuticals. **37.** Conti F, et al. *Clin Cases Miner Bone Metab.* 2017;14(2):230-234. **38.** Szabo SM, et al. Poster presented at: International Meeting of Pediatric Endocrinology; September 14-17, 2017; Washington, DC. **39.** Berkseth KE, et al. *Bone.* 2013;54(1):21-27. **40.** Whyte MP, et al. *Bone.* 2015;75:229-239. **41.** McKiernan FE, et al. *Osteoporos Int.* 2017;28(8):2343-2348. **42.** Drake MT, et al. *Mayo Clin Proc.* 2008;83(9):1032-1045. **43.** Sutton R, et al. J Bone Miner Res. 2012;27(5):987-994. **44.** Cundy T, et al. *J Bone Miner Res.* 2015;30(9):1726-1737. **45.** Whyte MP, et al. *J Clin Endocrinol Metab.* 2007;92(4):1203-1208. **46.** Laroche M. *Calcif Tissue Int.* 2012;90(3):250. **47.** Shapiro JR, Lewiecki EM. *J Bone Miner Res.* 2017;32:1977-1980. **48.** Talotta R, et al. *Clin Exp Rheumatol.* 2017;35(suppl 102):s6-s12. **49.** Kishnani PS, et al. *Mol Genet Metab.* 2017;122(1-2):4-17. **50.** Pirkle JL. CDC Laboratory Procedure Manual. https://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/vit_b6_e_met.pdf. Accessed March 27, 2018. **51.** Whyte MP, et al. *J Clin Invest.* 1985;76(2):752-756. **52.** Whyte MP. In: Bilezikian JP, et al, eds. *Principles of Bone Biology.* Vol 2. 3rd ed. San Diego, CA: Academic Press; 2008:1573-1598.

ALEXION®