WHEN KIDNEY STONES MAY BE A SIGN OF SOMETHING MORE SERIOUS[1,2]

Primary hyperoxaluria type 1 (PH1):
a metabolic stone disease with potentially devastating consequences.[2–4]

Alnylam® PHARMACEUTICALS

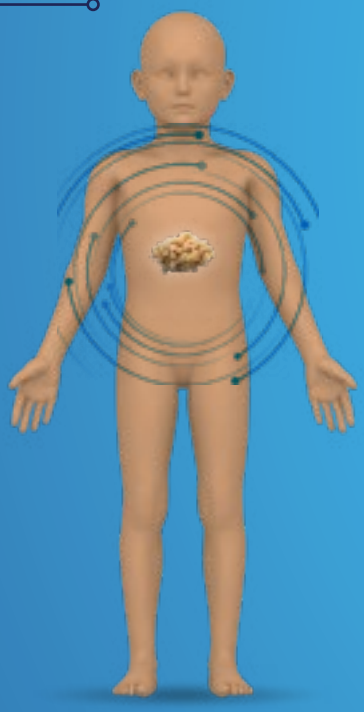
For healthcare professionals only. Sponsored and funded by Alnylam Pharmaceuticals.

When patients present with kidney stones, a metabolic stone disease may be the cause[1,2]

ANY UNUSUAL PRESENTATION AMONG STONE FORMERS MERITS FURTHER INVESTIGATION:[1]

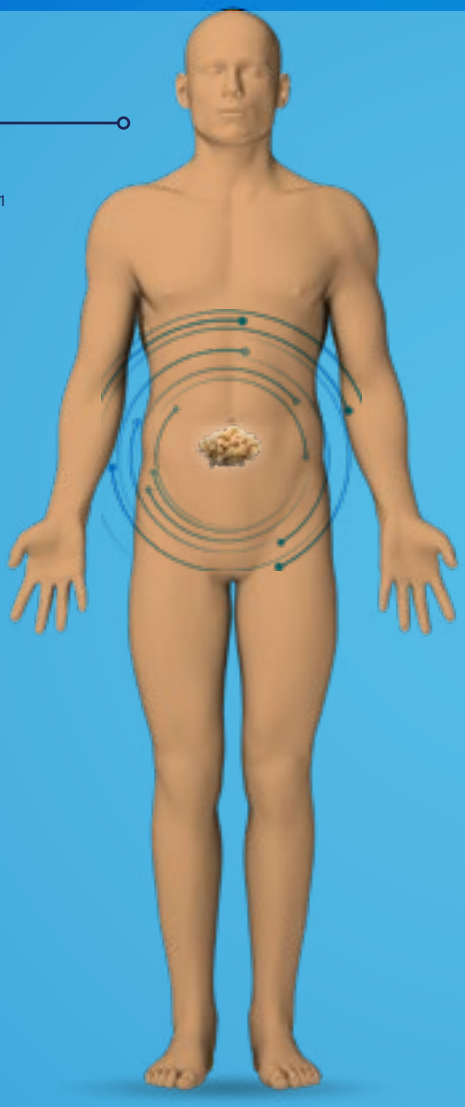
CHILD OR ADOLESCENT

- Any renal and bladder stone[1,5]
- Family history of stones[1]



ADULT

- Recurring stones[1]
- Multiple or bilateral stones[1]
- Stones may be larger on average, such as staghorn stones[1,6–9]
- Family history of stones[1]
- Biochemical composition (e.g., high proportion of calcium oxalate monohydrate, cystine, xanthine, uric acid)[1,10]



34% (n=175/511) of paediatric stones in a retrospective study were linked to a metabolic condition[11]

46%–57% p<0.05 is the heritability of the risk for kidney stone formation*,[12]

*As estimated based on twin studies.[12]

Almost 100% of children and 10% of adults who receive renal replacement therapy have an inherited kidney disease[13]

There are additional clinical red flags that, when also present, likely indicate a stone-forming, systemic condition:[1,3,14–16]

- Abnormal urinary chemistry on 24-hour urine test
  (e.g., high oxalate, low citrate, high magnesium, high calcium, high glycolate)[3,14–16]
- Impaired kidney function[1,3]
- End-stage renal disease (ESRD)[1,3]
- Nephrocalcinosis[1,3]
- Failure to thrive (infants)[1,3]
- Tubular dysfunction and related manifestations (mostly in children)
  (statural growth deficit, polyuria, bone disorders)[1]
- Extrarenal manifestations (mostly in children)
  (sensorineural hearing defects, ocular abnormalities, neurological disorders)[1]

***Genetic Testing:** In the workup of such patients, genetic testing may identify a mutation associated with kidney stone formation.[1,14]*

EXAMPLES OF METABOLIC STONE DISEASES[1,10,17]

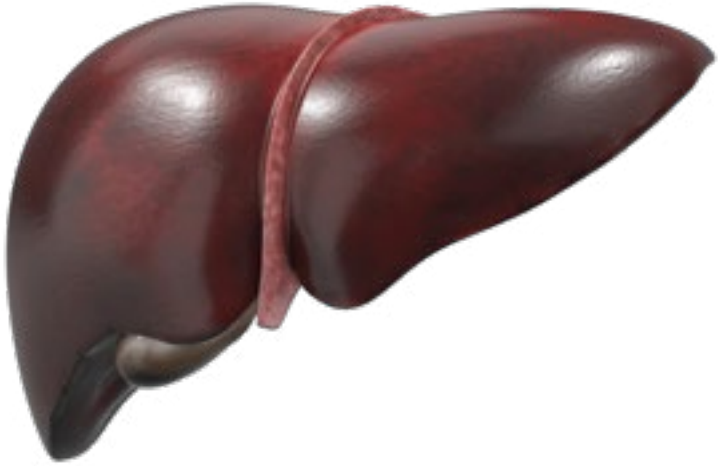
Primary hyperoxaluria	Cystinuria
Absorptive hypercalciuria	Xanthinuria
Dent disease	Renal hypouricaemia
Renal hypomagnesaemia	Distal renal tubular acidosis

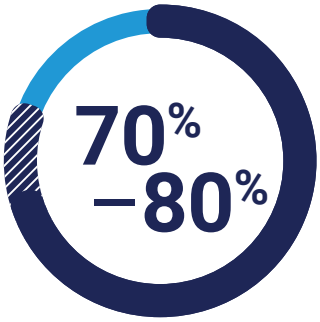
Kidney stones are the most common clinical manifestation that lead to a diagnosis of primary hyperoxaluria type 1 (PH1)[18]

thinkPH1

PH1: a potentially life-threatening and progressive genetic disease that often presents with kidney stones[2–4]

Primary hyperoxalurias (PHs) are a group of genetic diseases that lead to overproduction of oxalate in the liver[4]

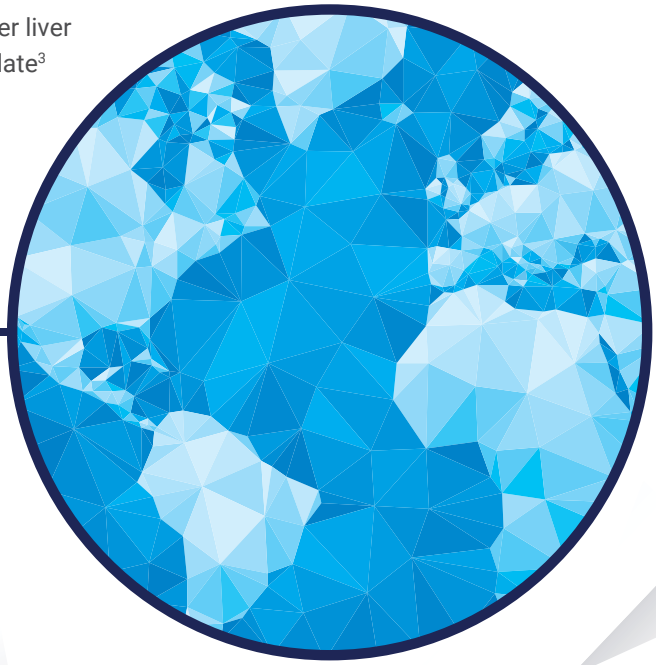




of all PH cases are the most severe type: PH1[2,4,19]

Although renal damage is a primary consequence, a genetic defect in the liver causes PH1[3,4]

- PH1 is caused by mutations in the *AGXT* gene which render the liver enzyme alanine:glyoxylate aminotransferase (AGT) dysfunctional[4,20]
  - In the absence of functional AGT, glyoxylate—made by another liver enzyme, glycolate oxidase (GO)—is instead converted to oxalate[3]
- One of the most devastating aspects of PH1 is that it results in a progressive decline in kidney function, typically culminating in ESRD[2,4]
  - Moreover, there is the potential risk of systemic oxalosis[4]



PH1 is rare, affecting approximately

1–3 OUT OF EVERY MILLION PEOPLE IN EUROPE AND NORTH AMERICA,

and has a higher prevalence in the Middle East and North Africa region[4,21]

Regardless of renal status, acute decline can occur suddenly, even in previously stable disease[9,22]

PH1 has heterogeneous clinical manifestations[2,3]

- Clinical manifestations can present at any age[3]
- PH1 patients with identical genotypes, and even members of the same family, can have variable disease presentations and different rates of progression[2]

PH1 PATIENTS MAY PRESENT WITH ONE OR MORE OF THE FOLLOWING CLINICAL MANIFESTATIONS:

Recurrent urolithiasis[2]

Kidney stone in a child[3]

Nephrocalcinosis[2,4,20]

Failure to thrive in infancy[3]

Progressive kidney function decline of unknown cause that commonly progresses to ESRD[2,4,20]

Family history of stones[20]

Though kidney stones are the most common clinical manifestation, there may be PH1 patients who are not stone formers[8,23]

PH1 is defined by a progressive decline in renal function with eventual advancement towards ESRD, though the rate is variable[3,8,24]

- In some instances, renal function can decline after a single incident of dehydration due to acute illness or intense physical activity[9,20,22,24–26]
  - This can occur even in patients with previously stable disease[22]

Continuous oxalate overproduction may cause progressive damage in the kidneys and other organs[8]

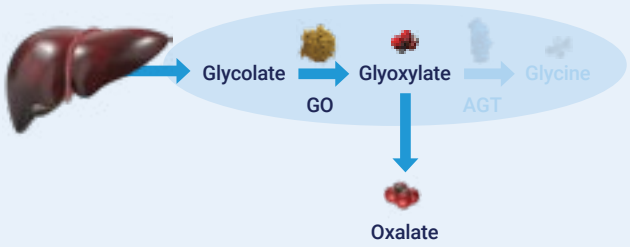
PH1 is an autosomal-recessive genetic disease that is caused by mutations in the *AGXT* gene[3,4]

- Mutations in the *AGXT* gene lead to a disruption in the pathway of the liver-specific enzyme AGT, which is normally involved in glyoxylate processing[3,4]
- The inability of AGT to process glyoxylate made by GO causes oxalate overproduction[3]

NORMALLY

AGT processes glyoxylate, which is generated by another liver enzyme, GO[3,4]

IN PH1



Due to dysfunctional AGT, glyoxylate is instead converted into oxalate, which cannot be metabolised[3,4]

PH1 CRYSTAL FORMATION FOLLOWS OXALATE OVERPRODUCTION[3,8]

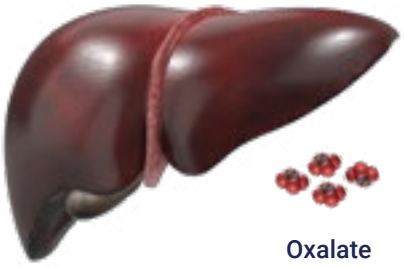
In the kidneys, oxalate combines with calcium, creating insoluble calcium oxalate crystals.[3]

These crystals attach to renal tissues, where they can aggregate to form kidney stones or lead to nephrocalcinosis.[8]

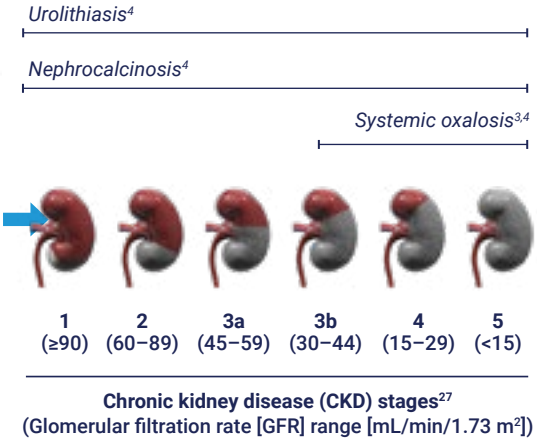
PH1 can be fatal, often due to complications of ESRD and/or systemic oxalosis[3,8]

LIVER OXALATE OVERPRODUCTION

Liver oxalate overproduction and subsequent accumulation may lead to inflammation and progressive kidney function decline.[8]

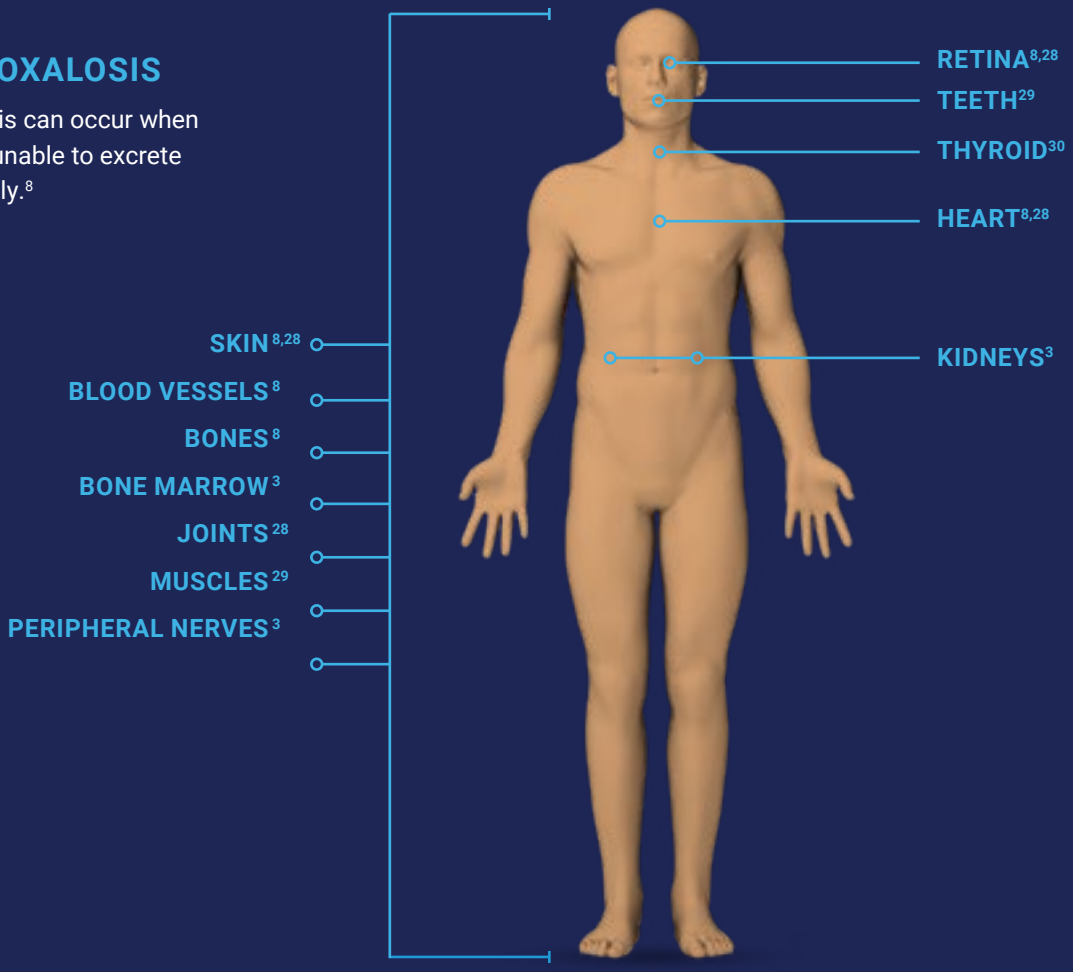


Oxalate



SYSTEMIC OXALOSIS

Systemic oxalosis can occur when the kidneys are unable to excrete oxalate effectively.[8]



As kidney function declines, oxalate excretion is compromised and calcium oxalate crystals deposit into tissues throughout the body[8]

thinkPH1

PH1 remains underdiagnosed in clinical practice[8,31–34]

- Historically, PH1 has a low index of suspicion due to:[8,31,32,34]
  - symptomatology that is nonspecific or shared with other diseases[32]
  - initially progressing without symptoms[8]
- **5.5 years is the median delay** in adults between onset of clinical manifestations and diagnosis[33]

of PH1 patients may be undiagnosed*[,34]

*Prevalence data are limited

Clinical manifestations may not be recognised.[8] Additionally, they may not be considered as indicative of PH1, delaying diagnosis until ESRD.[31,35–38]

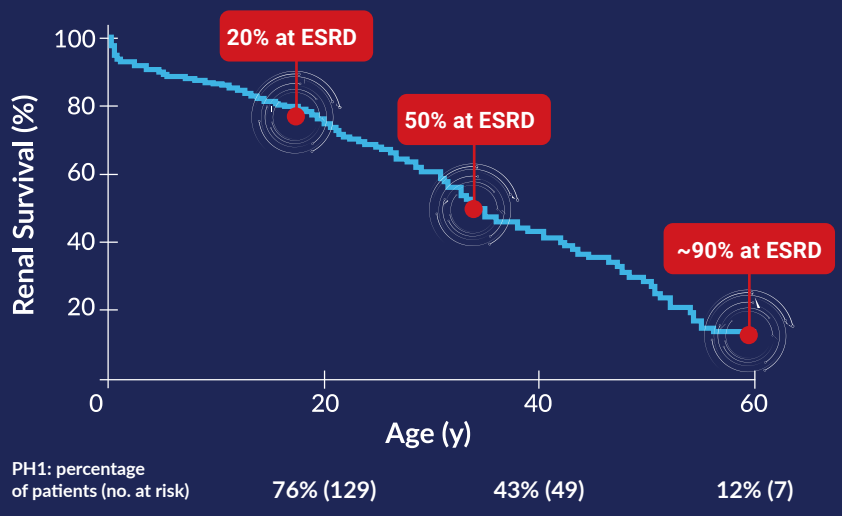
- Frequently, PH1 patients are already suffering from irreparable kidney damage when diagnosed, with **up to 70% of diagnoses in adults occurring after progression to ESRD**[31,35–38]
- Recurrent disease after kidney transplantation (or graft loss) may even occur before a conclusive diagnosis[34]

Progressive decline to ESRD occurs over time[*,34]*

- ***By adulthood (18 years old),*** *20% of patients will have progressed to ESRD*[34]
- ***Before the fourth decade of life,*** *50% of patients will have progressed to ESRD*[34]
- ***By age 60,*** *nearly all patients will have progressed to ESRD*[34]

*Poor renal survival in PH1 as demonstrated in a retrospective study that included 247 patients with PH1 from the Rare Kidney Stone Consortium Registry.[34]

Figure adapted from Hopp K, et al. J Am Soc Nephrol. 2015;26:2559–2570.



Given the progressive nature of the disease, early diagnosis and disease management are critical in PH1[3,8]

Diagnosing PH1 can be straightforward if you know what to look for[20,30]

Evaluating a patient's family and medical history is helpful in identifying PH1[20,23]

Given the inherited nature of the disease, it is critical to screen all immediate relatives of a PH1 patient[8,20]

PH1 DIAGNOSIS

IN PATIENTS WITH PRESERVED RENAL FUNCTION

- A 24-hour urine test can raise suspicion of primary hyperoxaluria by measuring elevated oxalate levels, a biochemical hallmark of the disease[14,20,30]
- Normal urinary oxalate level (all ages):[2] <0.50 mmol (<45 mg)/1.73 m^2/day

IN PATIENTS WITH COMPROMISED RENAL FUNCTION

- Diagnostic workup for PH1 includes plasma oxalate measurement, a different approach than for patients with preserved renal function[8,20,39]
- Normal plasma oxalate level: <1.6 µmol/L*[,40]

*Reference values have not been established for patients under 21 or greater than 81 years of age.[40]

REGARDLESS OF RENAL STATUS

- Genetic testing is important as it can establish a PH1 diagnosis with high sensitivity and specificity[20,41]
- **Identifying *AGXT* gene mutations confirms PH1[20]**

Genetic testing to confirm a PH1 diagnosis is recommended by the European Hyperoxaluria Consortium OxalEurope and the American Urological Association (AUA)[14,20]

think PH1

Medical management options aim to delay progressive renal function decline[4]

Disease-mitigating strategies can lessen damage by reducing stone formation and renal deposition of calcium oxalate crystals, underscoring the importance of early diagnosis and intervention.[2,4,39]

MEDICAL MANAGEMENT OPTIONS

Hyperhydration[4]

- More than 2 to 3 litres per square metre of body surface area is the recommended daily fluid intake[4]
- To ensure constant urine dilution in infants, a gastrotomy tube may be necessary[4]

High dose pyridoxine (vitamin B6) therapy and calcium oxalate crystallisation inhibitors such as alkali citrate[4,20]

- Very few PH1 patients are complete responders to vitamin B6 and a subset of patients show a partial response, although data are limited, with only one prospective trial published to date (n=12)[3,20,42]

Intensive dialysis strategies beyond conventional methods[3]

- Dialysis either serves as a bridge to transplantation or as an adjunct therapy after dual liver-kidney transplantation[3]
- To reduce plasma oxalate levels, PH1 patients with compromised renal function may require up to 6 haemodialysis sessions per week, which may need to be combined with continuous peritoneal dialysis[3,20,43,44]
- Intensive dialysis is inadequate to consistently lower plasma oxalate[4,43]

The above medical management options rarely address the underlying pathophysiology of PH1 and most are inadequate at overcoming oxalate overproduction.[3,20,43]

Liver or dual liver-kidney transplant: Only liver transplantation resolves the underlying metabolic defect[20]

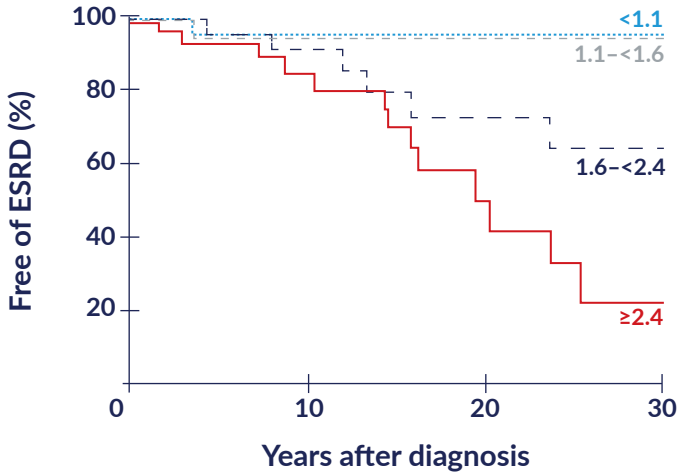
When a patient is diagnosed with PH1, they may have already progressed to ESRD and require a dual liver-kidney transplant. This procedure carries significant morbidity and mortality risks.[3,4,20]

There is an urgent need for new treatment options[45,46]

Additional treatment options that reduce liver oxalate overproduction in PH1 are needed[46]

Lower urinary oxalate (UOx) excretion predicted improved renal survival in a retrospective study that included 192 patients with PH1 from the Rare Kidney Stone Consortium Registry.[46]

HIGHER URINARY OXALATE LEVELS ARE ASSOCIATED WITH FASTER PROGRESSION TO ESRD*,[46]



UOx (mmol/1.73 m²/24 hours)	Survival estimate (no. at risk)			
<1.1	100 (42)	96 (7)	96 (1)	
1.1–<1.6	100 (42)	95 (8)	95 (5)	95 (2)
1.6–<2.4	100 (42)	91 (19)	73 (10)	65 (6)
≥2.4	100 (42)	85 (19)	42 (6)	23 (2)

Among patients who did not have ESRD at diagnosis, renal survival estimates were lowest for patients with UOx excretion ≥2.4 mmol/1.73 m²/24 hours (HR=3.4 [95% CI: 1.4–7.9]; *p*=0.005).[46]

Figure adapted from Zhao F, et al. Clin J Am Soc Nephrol. 2016;11:119–126.

RESEARCH IS ONGOING

There are a number of investigational therapies in development for PH1.[47–50]

Oxalate synthesis pathway inhibitors[47,48]

Prevent expression or activity of enzymes involved in oxalate production:[47,48]

- RNA interference (RNAi) therapeutics bind to messenger RNA of target enzymes, preventing their expression via the RNAi pathway[47]
- Enzyme inhibitors suppress enzymatic activity[48]

Oxalate degraders[49,50]

Live biotherapeutic products and crystalline formulations degrade oxalate in the gastrointestinal tract.[49,50]

thinkPH1

CONSIDER GENETIC TESTING FOR YOUR PATIENTS

when you suspect a metabolic stone disease such as PH1[2,4]

For you: visit thinkPH1.eu for more information.
For your patients: direct them to livingwithPH1.eu for support and information about PH1.

Please visit alnylamconnect.eu to sign up to receive further information about primary hyperoxaluria type 1 (PH1) from Alnylam.

References: 1. Ferraro PM, D'Addessi A, Gambaro G. *Nephrol Dial Transplant*. 2013;28(4):811–820. **2.** Hoppe B. *Nat Rev Nephrol*. 2012;8(8):467–475. **3.** Milliner DS, Harris PC, Cogal AG, Lieske JC. https://www.ncbi.nlm.nih.gov/books/NBK1283/. Updated February 10, 2022. Accessed June 28, 2023. **4.** Cochat P, Rumsby G. *N Engl J Med*. 2013;369(7):649–658. **5.** Hoppe B, Kemper MJ. *Pediatr Nephrol*. 2010;25:403–413. **6.** Jendeberg J, Geijer H, Alshamari M, Cierzniak B, Lidén M. *Eur Radiol*. 2017;27(11):4775–4785. **7.** Carrasco A Jr, Granberg CF, Gettman MT, Milliner DS, Krambeck AE. *Urology*. 2015;85(3):522–526. **8.** Hoppe B, Beck BB, Milliner DS. *Kidney Int*. 2009;75(12):1264–1271. **9.** Leumann E, Hoppe B. *J Am Soc Nephrol*. 2001;12:1986–1993. **10.** Sperling O. *Mol Genet Metab*. 2006;89(1–2):14–18. **11.** Issler N, Dufek S, Kleta R, Bockenhauer D, Smeulders N, van't Hoff W. *BMC Nephrology*. 2017;18(36):1–8. **12.** Goldfarb DS, Avery AR, Beara-Lasic L, Duncan GE, Goldberg J. *Kidney Int Rep*. 2019;4(4):535–540. **13.** Devuyst O, Knowers NVAM, Remuzzi G. *Lancet*. 2014;383(9931):1844–1859. **14.** American Urological Association. https://www.auanet.org/guidelines-and-quality/guidelines/kidney-stones-medical-mangement-guideline. Published 2019. Accessed June 28, 2023. **15.** Zuckerman JM, Assimos DG. Rev Urol. 2009;11(3):134–144. **16.** Konrad M, Hou J, Weber S, et al. *J Am Soc Nephrol*. 2008;19(1):171–181. **17.** Worcester EM, Coe FL. *Prim Care*. 2008;35(2):369-vii. **18.** Hoppe B, Langman CB. *Pediatr Nephrol*. 2003;18:986–991. **19.** Rare Kidney Stone Consortium. http://www.rarekidneystones.org/hyperoxaluria/. Published July 2015. Accessed June 28, 2023 **20.** Cochat P, Hulton SA, Acquaviva C, et al. *Nephrol Dial Transplant*. 2012;27(5):1729–1736. **21.** Bhasin B, Ürekli HM, Atta MG. *World J Nephrol*. 2015;4(2):235–244. **22.** El-Reshaid K, Al-Bader D, Madda JP. *Saudi J Kidney Dis Transpl*. 2016;27(3):606–609. **23.** Edvardsson VO, Goldfarb DS, Lieske JC, et al. *Pediatr Nephrol*. 2013;28(10):1923–1942. **24.** Jamieson NV. *Am J Nephrol*. 2005;25:282–289. **25.** Harambat J, Fargue S, Bacchetta J, Acquaviva C, Cochat P. Int *J Nephrol*. 2011;2011:864580. **26.** Tintillier M, Pochet JM, Cosyns JP, Delgrange E, Donckier J. *Clin Nephrol*. 2004;62(2):155–157. **27.** Drawz P, Rahman M. *Ann Intern Med*. 2015;162(11):ITC1-ITC16. **28.** Falk N, Castillo B, Gupta A, McKelvy B, Bhattacharjee M, Papasozomenos S. *Ann Clin Lab Sci*. 2013;43(3):328–331. **29.** Lorenz EC, Michet CJ, Milliner DS, Lieske JC. *Curr Rheumatol Rep*. 2013;15(7):340. **30.** Ben-Shalom E, Frishberg Y. *Pediatr Nephrol*. 2015;30(10):1781–1791. **31.** Harambat J, Fargue S, Acquaviva C, et al. *Kidney Int*. 2010;77:443–449. **32.** Hulton SA. *Int J Surg*. 2016;36:649–654. **33.** van der Hoeven SM, van Woerden CS, Groothoff JW. *Nephrol Dial Transplant*. 2012;27:3855–3862. **34.** Hopp K, Cogal AG, Bergstralh EJ, et al. *J Am Soc Nephrol*. 2015;26:2559–2570. **35.** van Woerden CS, Groothoff JW, Wanders RJA, Davin JC, Wijburg FA. *Nephrol Dial Transplant*. 2003;18:273–279. **36**. Mandrile G, van Woerden CS, Berchialla P, et al; for OxalEurope Consortium. *Kidney Int*. 2014;86(6):1197–1204. **37.** Lieske JC, Monico CG, Holmes WS, et al. *Am J Nephrol*. 2005;25:290–296. **38.** Soliman NA, Nabhan MM, Abdelrahman SM, et al. *Nephrol Ther*. 2017;13(3):176–182. **39**. Raju DL, Cantarovich M, Brisson ML, Tchervenkov J, Lipman ML. *Am J Kidney Dis*. 2008;51(1):e1–e5. **40.** Mayo Clinic Laboratories. https://www.mayocliniclabs.com/test-catalog/overview/606472#Clinical-and-Interpretive. Accessed June 28, 2023. **41.** Williams EL, Bagg EA, Mueller M, Vandrovcova J, Aitman TJ, Rumsby G. *Mol Genet Genomic Med*. 2015;3(1):69–78. **42.** Hoyer-Kuhn H, Kohbrok S, Volland R, et al. *Clin J Am Soc Nephrol*. 2014;9:468–477. **43.** Cochat P, Fargue S, Harambat J. *Curr Opin Organ Transplant*. 2010;15:590–593. **44.** Plumb TJ, Swee ML, Filaus JA. *Am J Kidney Dis*. 2013;62(6):1155–1159. **45.** Rare Diseases Working Group. Addressing unmet needs in the PH1 patient population. Accessed 19 July 2023. https://admin.allianceforpatientaccess.org/wp-content/uploads/2022/11/AfPA_Addressing-Unmet-Needs-in-the-PH1-Populations_Report_October2022.pdf **46.** Zhao F, Bergstralh EJ, Mehta RA, et al. *Clin J Am Nephrol*. 2016;11:119–126. **47.** Lai C, Pursell N, Gierut J, et al. *Mol Ther*. 2018;26(8):1983–1995. **48.** Le Dudal M, Huguet L, Perez J, et al. *J Clin Invest*. 2019;129(6):2571–2577. **49.** Kaufman DW, Kelly JP, Curhan GC, et al. *J Am Soc Nephrol*. 2008;19:1197–1203. **50.** Albert A, Tiwari V, Paul E, et al. *J Enzyme Inhib Med Chem*. 2017;32(1):426–433.

July 2023 PH1-CEMEA-00120

Alnylam® PHARMACEUTICALS