Managing **Primary Hyperoxaluria Type 1**

Alnylam PHARMACEUTICALS

Primary hyperoxaluria type 1 (PH1) is an ultra-rare, debilitating, inherited condition that typically presents in childhood and is characterized by painful kidney stones, often inevitable progression to end-stage kidney disease (ESKD) and increased morbidity and mortality.[1,2]

Cause of PH1[1,2]

PH1 is caused by mutations in the *AGXT* gene that render the liver enzyme alanine-glyoxylate aminotransferase (AGT) dysfunctional. AGT, when functional, helps rid the body of unwanted products of normal metabolism. In people with PH1, defective AGT causes an abnormal accumulation of oxalate — a waste product not used by the body — initially in the kidneys, and, when the disease advances, in other organs.

Role of oxalate in PH1[4]

Even in the absence of overt symptoms, oxalate is constantly being overproduced and can cause irreparable damage to the kidneys.

Oxalate is an end product of metabolism.

Oxalate **accumulates in the kidneys,** forming calcium oxalate crystals.

As nephrocalcinosis occurs, renal impairment causes crystals to be deposited throughout the body, **damaging kidneys and major non-kidney organs.**

High levels of oxalate are toxic, and cannot be broken down by the body.

The crystals attach to renal tissues, where they can aggregate to **form kidney stones or lead to renal deposition of calcium oxalate crystals (nephrocalcinosis).**

PH1 Facts

PH1 is an ultra-rare:

1-3 per million

people diagnosed in North America and the EU[2,3]

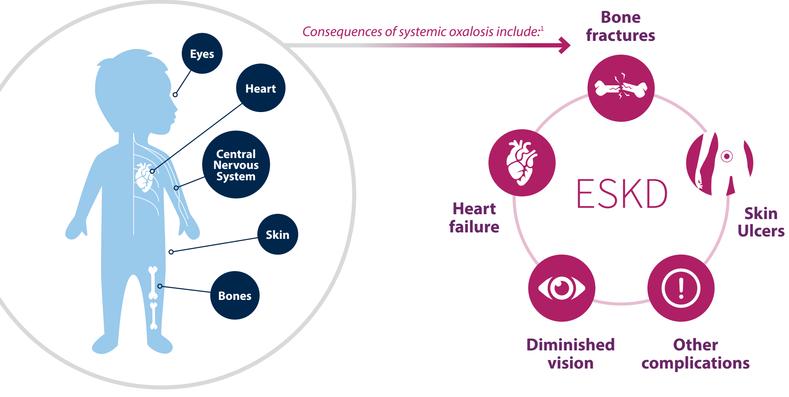
Onset typically in **early childhood**[1]

Majority of people living with PH1 present with kidney stones. Kidney stones can result in:[1]

- **Flank pain**
- **Urinary tract infections**
- **Painful urination**
- **Blood in the urine**
- **Surgery for removal**

ESKD is a looming threat for people living with PH1[2,5]

PH1 can ultimately result in ESKD, a life-threatening condition also known as kidney failure that prevents the kidneys from functioning properly.[2] Once kidney function has been compromised, oxalate can spread throughout the body, resulting in systemic oxalosis wherein oxalate crystals can deposit in the eyes, skin, bones, heart and central nervous system of people with PH1.[2]



UP TO **70%** **of people diagnosed** with PH1 present with ESKD[6,7,8,9,10]

For example, children, adults and caregivers of those with PH1 experience the anxiety of not knowing:[11]

- **When will the next painful kidney stone episode occur?**
- **How long will their or their loved one's kidneys keep working?**
- **Will they/their child/loved one need to undergo an organ transplant?**

Diagnosing PH1

Inaccurate diagnoses pose a high risk of irreversible damage. Given the ultra-rare nature of the disease and symptoms that are often mistaken for that of other conditions, PH1 is frequently under– or misdiagnosed. Early diagnosis is crucial and may allow for appropriate management of symptoms.[7,9,10,12,13]

~**50%** of people living with PH1 may be undiagnosed, although data on prevalence are limited[6]

5.5 YEARS is the median delay in adults between onset of clinical manifestations and diagnosis[13]

Guidelines recommend metabolic testing including **24-hour urine collection.**[5] Spot urine measurements may be appropriate when 24-hour urine collections cannot be collected. Plasma oxalate measurements may be appropriate in patients with impaired kidney function.[5]

In appropriate patients with elevated urinary or plasma oxalate, **genetic testing may help confirm PH1**[1,14]

For more information on PH1, visit Alnylam.com

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