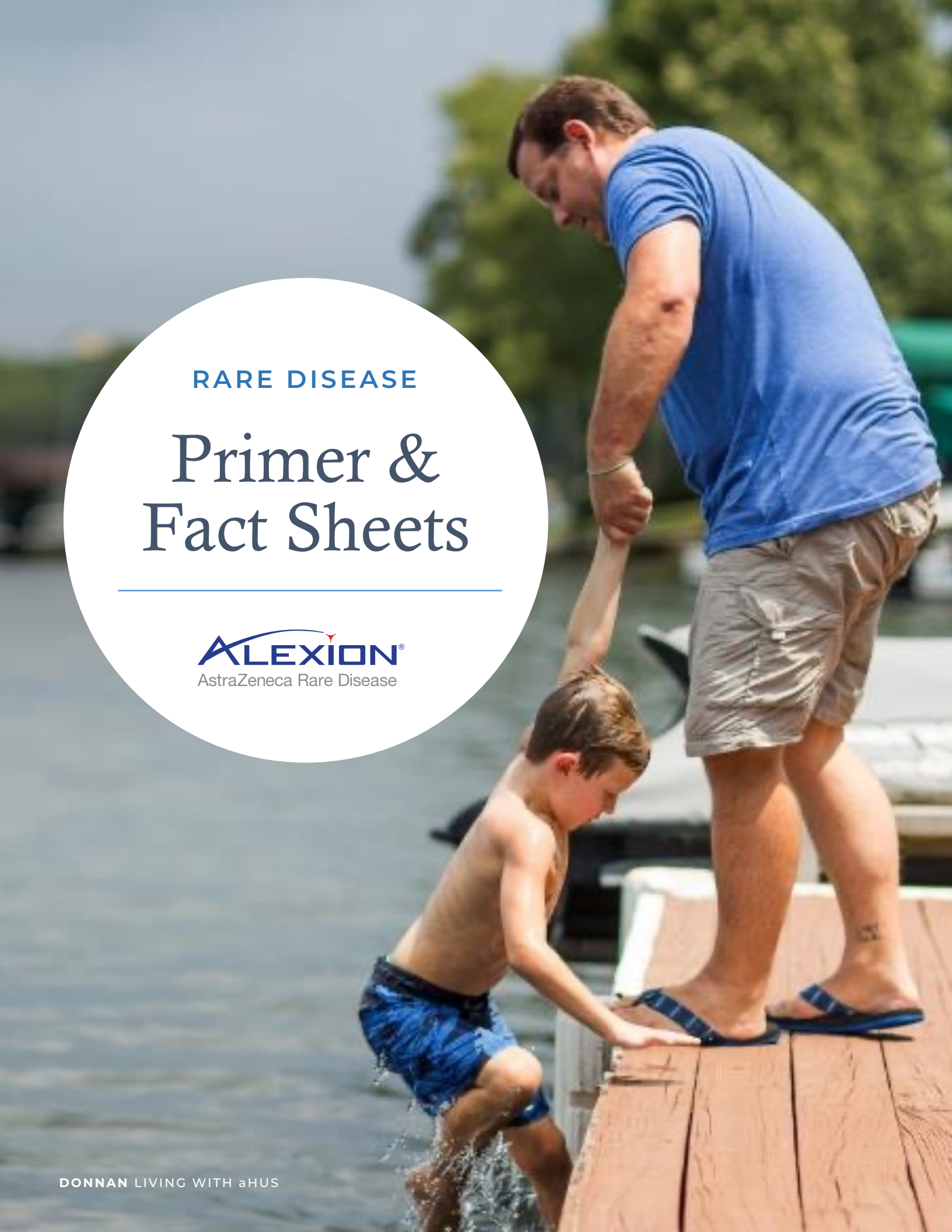


RARE DISEASE

Primer & Fact Sheets

ALEXION®
AstraZeneca Rare Disease

Rare and Ultra-Rare Diseases

Rare diseases can be difficult to diagnose and devastating to live with. Although rare diseases affect a small number of people, the impact on patients, their families, and society is profound, as many are severe, chronic and progressive. Patients often live without hope, as they may face premature death without effective treatment options.

Approximately **300 million** people worldwide live with a rare disease.[1]

In the United States, a rare disease affects fewer than **200,000 people** (or about 620 patients per million of population).[2,3]

In Europe, a rare disease affects **1 in 2,000 people** (or about 500 patients per million of population).[4]

In Europe, a disease is generally considered to be ultra-rare if it affects **one patient per 50,000 people** (or fewer than 20 patients per million of population).[5]

There are approximately **7,000 rare diseases**, but only about 5% of them have treatment options available.[6,7]

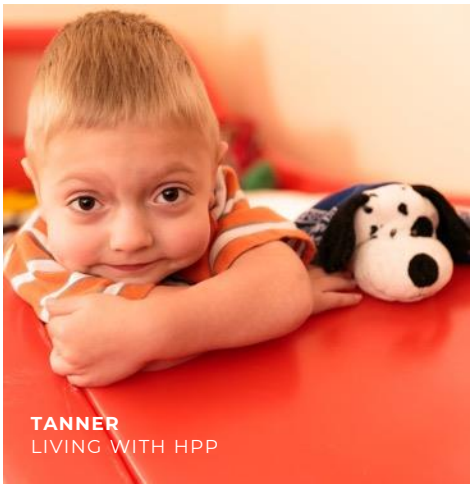
> **"When I shared my story, I realized it's important to know you are not alone and that there is hope. It gave me a sense of comfort and encouragement. Now, I know that others can benefit from my experience, and I want to be an inspiration to them."**
>
> **VICTOR**
> LIVING WITH PNH

References:

1. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. European Journal of Human Genetics. September 2019. Accessed at: https://www.nature.com/articles/s41431-019-0508-0. Accessed online May 28, 2020.
2. US Food and Drug Administration's Definition of Disease Prevalence for Therapies Qualifying Under Orphan Drug Act. Accessed at: https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=91b7be5e87481538e33a4c0a76ba7183&n=21y5.0.1.1.6.3%20&r=SUBPART&ty=HTML. Accessed online May 28, 2020.
3. United States Census Bureau. Quick Facts. Accessed at: https://www.census.gov/quickfacts/fact/table/US/PST045219. Accessed online May 27, 2020.
4. Orphanet. About Rare Diseases. Accessed at: https://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN. Accessed online June 5, 2020.
5. REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/ EC. Accessed at: http://eur-lex.europa.eu/legal-content/EN/TXT/ PDF/?uri=CELEX:32014R0536&qid=1421232837997&from=EN. Accessed online May 28, 2020.
6. Global Genes, Rare Disease: Facts and Statistics. Accessed at: https://globalgenes.org/rare-facts/?gclid=EAIaIQobChMIwcyl3eSu6QIVCUqGCh1x6go2EAAYASACEgLQ9_D_BwE. Accessed online May 28, 2020.
7. Orphan Drugs in the United States - Providing Context for Use and Cost. Quintiles IMS Institute. October 2017. Accessed at: https://rarediseases.org/wp-content/uploads/2017/10/Orphan-Drugs-in-the-United-States-Report-Web.pdf. Accessed online May 26, 2020.

ALEXION®

Rare and Ultra-Rare Diseases



> **"My hope for Tanner in the future is that he enters into adulthood. I think that he's very smart, and I think that he is definitely going to go to college. I kind of hope that he will be a doctor, and maybe help kids like doctors have helped him."**
>
> **RENÉ**
> TANNER'S MOM

Challenges of Diagnosis, Drug Development and Treatment

Diagnosis

- Often, very few physicians are familiar with diagnosing and treating these illnesses, leading to missed, delayed or inaccurate diagnoses.
- Few researchers or companies explore the disease, due to the very small number of patients affected.
- Enhanced diagnostic tools and dissemination of knowledge are needed to improve treatments.

Drug Development & Treatment

- It can be difficult for investigators to identify appropriate patients who qualify for enrollment in ongoing rare disease clinical trials.
- The cost and risk associated with manufacturing orphan drugs increases, since most are complex biologics requiring living cells (production is simpler and less expensive with chemical drugs).

Helpful Resources

When a patient is diagnosed with a rare or ultra-rare disease, having a support system can be just as important as having the right physician and treatment plan. Several groups provide resources and support:

- **Global Genes** is a non-profit patient advocacy organization working to eliminate challenges of rare disease.
- **National Organization for Rare Disorders (NORD)** is a U.S.-based non-profit advocacy organization dedicated to helping people with rare diseases and assisting the organizations that serve them.
- **European Organisation for Rare Diseases (EURORDIS)** is a non-governmental patient-driven alliance of patient organizations representing 700+ rare disease patient organizations in 63 countries.
- **RareConnect** is an initiative of EURORDIS in which rare disease patients, families and patient organizations can develop online communities and conversations across continents and languages.
- **Orphanet** is a database of information on rare diseases and orphan drugs for the public.

Visit Alexion.com for more information about the rare and ultra-rare diseases we focus on.

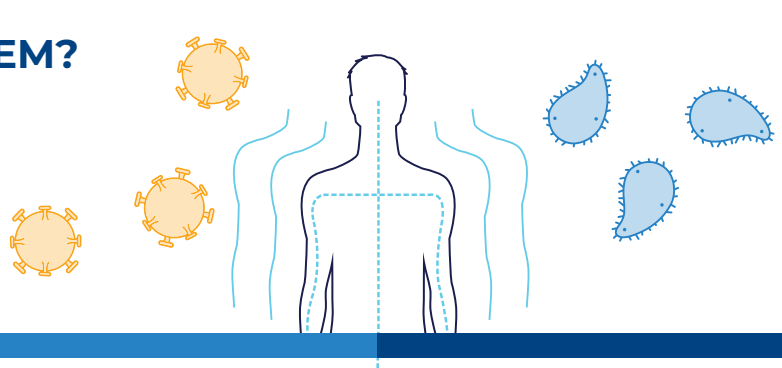
ALEXION®

Understanding the **Complement System**

ALEXION
AstraZeneca Rare Disease

WHAT IS THE IMMUNE SYSTEM?

The immune system is a complex network of organs, cells and proteins which work together to protect the body against infection and disease.



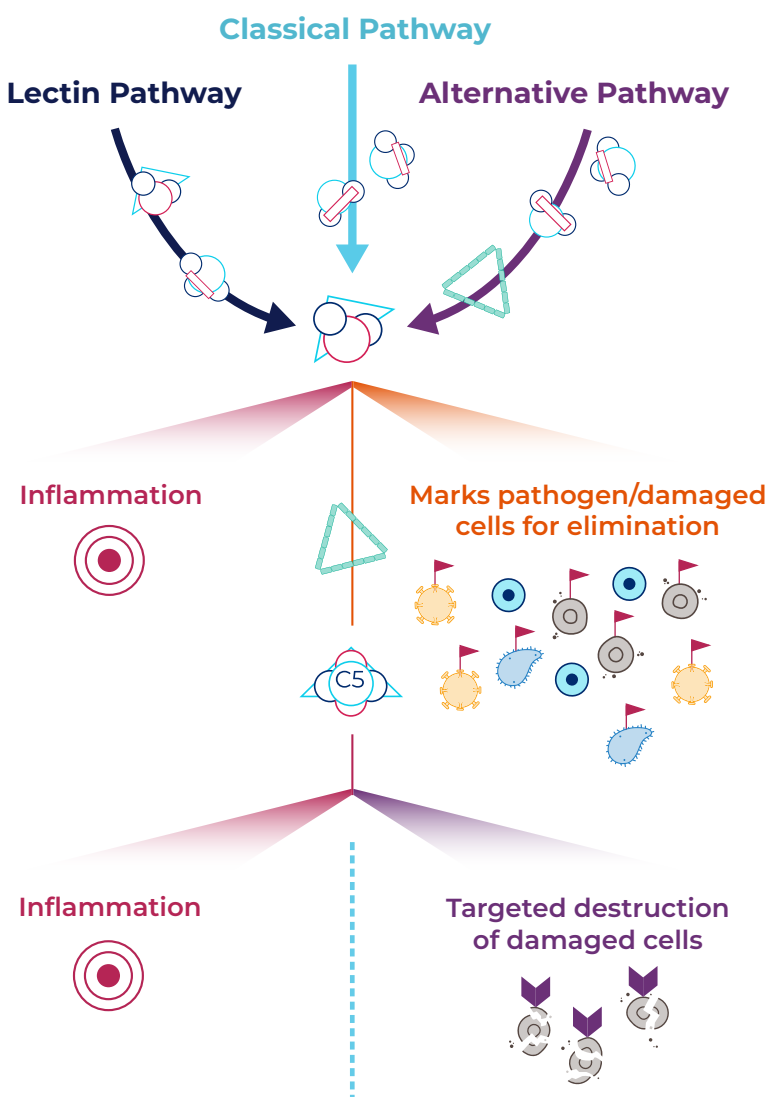
WHAT IS THE COMPLEMENT SYSTEM?

The complement system is a part of the immune system and is essential to the body's defense against infection.

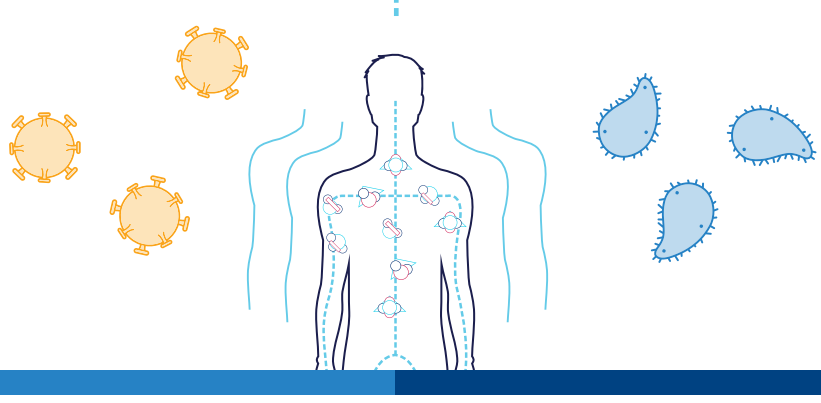
Made up of
3 UNIQUE PATHWAYS
(Classical, Lectin and Alternative)

Each pathway can become **activated to trigger a cascade of protein reactions** that initiate an immune response to detect and eliminate:

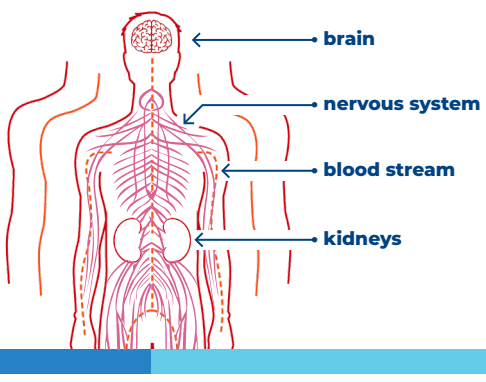
- **Bacteria**
- **Viruses**
- **Dead cells**



When the complement system is working properly, it is a strong and powerful tool that **protects the body** against harmful invaders.



But when the system is thrown out of balance, or dysregulated, the proteins can **trigger a dangerous, uncontrolled cascade of reactions that attack cells** and tissues.



UNLOCKING THE POTENTIAL OF THE COMPLEMENT SYSTEM

Alexion's pioneering legacy in rare diseases is rooted in being the first to translate the complex biology of the complement system into transformative medicines.

3 DECADES
of complement inhibition research

20 YEARS
of real-world evidence demonstrating the safety and power of targeted complement inhibitors

Dysregulation of the complement system is a key driver of many devastating diseases. Alexion has paved the way for a new class of medicines that inhibit the complement system, prevent further damage and reduce disease symptoms.

Alexion is committed to continue unlocking the potential of the complement system and accelerating the **discovery and development of new life-changing therapies for even more patients**.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

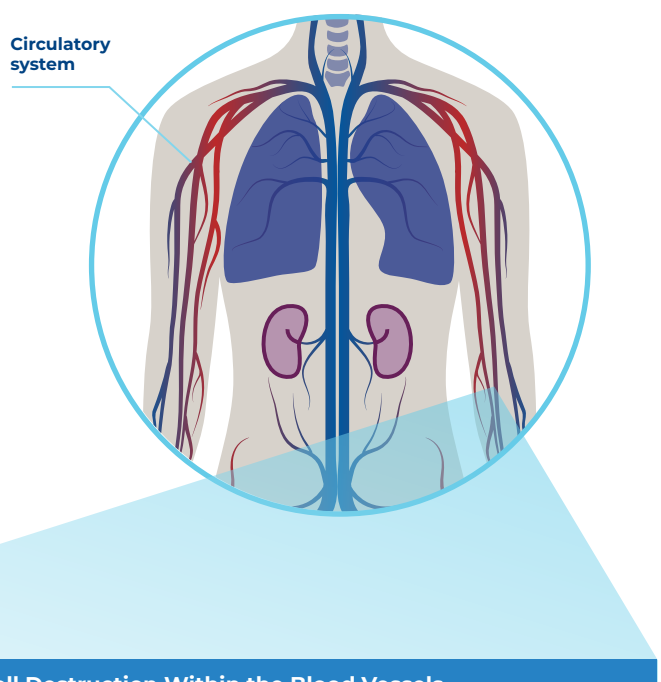
ALEXION
AstraZeneca Rare Disease

WHAT IS PNH?

Paroxysmal nocturnal hemoglobinuria (PNH) is a **rare, chronic, progressive, and potentially life-threatening blood disorder.**

PNH is characterized by **red blood cell (RBC) destruction** within blood vessels (also known as **intravascular hemolysis**, or IVH) and **white blood cell and platelet activation**, which may lead to blood clots (thrombosis).

PNH is caused by an **acquired genetic mutation** (not inherited) that may happen any time after birth and results in the **production of abnormal blood cells** that are **missing important protective blood cell surface proteins**. These missing proteins enable the complement system to 'attack' and **destroy or activate these abnormal blood cells**.[1-3]



PNH is estimated to affect approximately **16-20 people per million worldwide**.[4]

PNH can occur in **children and adults** at any age; the average age of diagnosis is in the **early 30s**.[5]

PNH affects both **men and women** and people of **every racial and ethnic group**.[5]

Living with PNH can be debilitating, and signs and symptoms may include[1,6,7]

- **Blood clots (thrombosis)**
- **Abdominal pain**
- **Difficulty swallowing**
- **Erectile dysfunction**
- **Shortness of breath**
- **Excessive fatigue**
- **Anemia**
- **Dark-colored urine (hemoglobinuria)**

PNH can lead to **thrombosis**, which can occur in blood vessels throughout the body, and/or damage to other vital organs, such as **kidneys and lungs**. This can result in an overall **impaired quality of life** and **potentially premature death**.[8,9]

HOW IS PNH DIAGNOSED AND MONITORED?

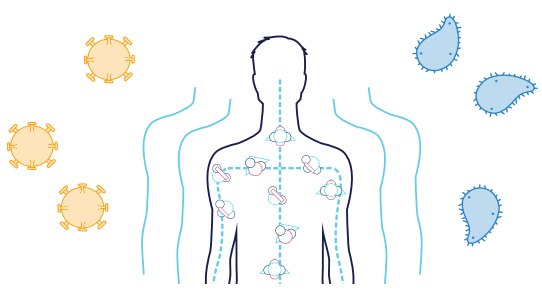
Diverse symptoms and varied clinical presentation can delay diagnosis by up to **10 years**.[8]

PNH can be **diagnosed from a simple blood test** (high-sensitivity flow cytometry), which can detect and count PNH blood cells.[10]

Another type of blood test is used to **monitor ongoing PNH disease activity**. This test measures lactate dehydrogenase (LDH), an enzyme that is released from red blood cells during IVH.

Monitoring LDH regularly is a very important part of managing PNH. If high levels of LDH are present, it means that many red blood cells have been destroyed within blood vessels. This has been shown to correlate with complications, such as thrombosis and early mortality.

THE COMPLEMENT SYSTEM



The complement system is a part of the immune system and is **essential to the body's defense against infection**.[13]

When the system is **thrown out of balance**, or dysregulated, these proteins can **trigger a dangerous, uncontrolled cascade of reactions** that attack cells and tissues resulting in **harmful inflammation** and the **destruction of healthy cells**.[14]

WHAT ROLE DOES COMPLEMENT INHIBITION PLAY IN TREATING PNH?

In PNH, **immediate, complete and sustained terminal complement inhibition** (by blocking the C5 protein) is the proven standard of care to **prevent the destruction of PNH red cells and activation of PNH white cells and platelets**. This helps reduce symptoms and complications and improve survival, transforming the lives of those impacted by PNH.

Alexion's leadership in complement inhibition has set the course for the continued study and development of innovative treatments for certain rare complement-mediated diseases, including PNH.

WHAT TREATMENT APPROACH IS BEING STUDIED BY ALEXION?

In addition to developing the **first approved therapy for PNH**, Alexion aims to uncover new innovations and **provide additional treatment options** for those impacted by this devastating disease. Alexion is conducting **ongoing clinical trials** in PNH to investigate the safety and efficacy of blocking **Factor D**, another complement system protein, as well as **new treatment delivery choices**.

We continue to **advance the understanding of PNH** and accelerate the **development of innovative life-changing therapies**.

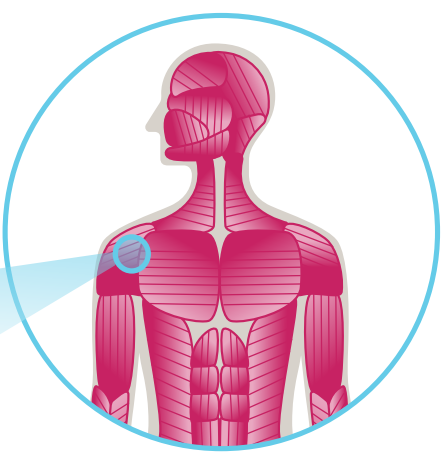
References:

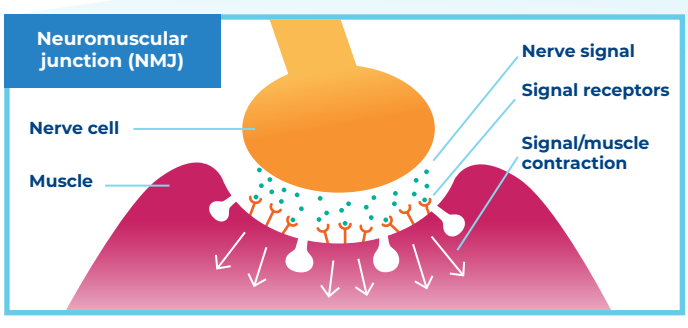
1. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014;124(18):2804-2811.
2. Holguin MH, et al. Isolation and characterization of a membrane protein from normal human erythrocytes that inhibits reactive lysis of the erythrocytes of paroxysmal nocturnal hemoglobinuria. J Clin Invest. 1989;84(1):7 17.
3. Jang, J. H., et al. (2016). Predictive Factors of Mortality in Population of Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH): Results from a Korean PNH Registry. Journal of Korean medical science, 31(2), 214–221.
4. Anita Hill, et al. The Incidence and Prevalence of Paroxysmal Nocturnal Hemoglobinuria (PNH) and Survival of Patients in Yorkshire. *Blood* 2006; 108 (11): 985.
5. Hill, A., Richards, S. J., & Hillmen, P. (2007). Recent developments in the understanding and management of paroxysmal nocturnal haemoglobinuria. British journal of haematology, 137(3), 181–192.)
6. Hillmen, P., et al. (2007). Effect of the complement inhibitor eculizumab on thromboembolism on patients with paroxysmal nocturnal hemoglobinuria. Blood, 110(12), 4123-4128.
7. Kulasekararaj, A. G., et al. (2019). Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood, 133(6), 540–549.
8. Hillmen, P., et al. (1995). Natural history of paroxysmal nocturnal hemoglobinuria. The New England journal of medicine, 333(19), 1253–1258.
9. O'Connell, T., et al. (2020). Cost-Utility Analysis of Ravulizumab Compared with Eculizumab in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria. PharmacoEconomics, 38(9), 981–994
10. Fletcher M, et al. Current international flow cytometric practices for the detection and monitoring of paroxysmal nocturnal haemoglobinuria clones: A UK NEQAS survey. Cytometry B Clin Cytom. 2017;92(4):266-274.
11. Jang JH, Kim JS, Yoon SS, et al. Predictive factors of mortality in population of patients with paroxysmal nocturnal hemoglobinuria (PNH): results from a Korean PNH registry. J Korean Med Sci. 2016;31(2):214-221.
12. Lee, J. W., et al. (2019). Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood, 133(6), 530–539.
13. Merle, N. S., et al. (2015). Complement System Part II: Role in immunity. Frontiers of Immunology, 6:257.
14. Garred, P., Tenner, A. J., & Mollnes, T. E. (2021). Therapeutic Targeting of the Complement System: From Rare Diseases to Pandemics. Pharmacological Reviews, 73(2) 792-827.

Generalized myasthenia gravis (gMG)

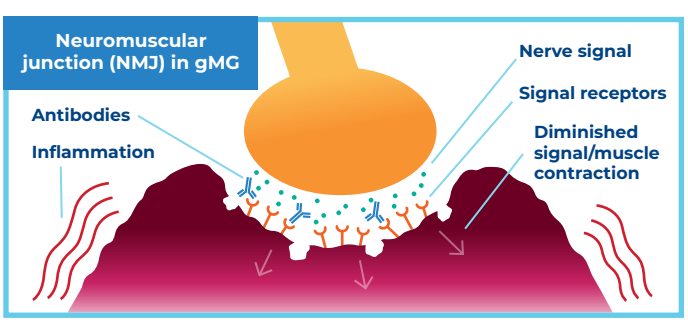
WHAT IS GENERALIZED MYASTHENIA GRAVIS?

Generalized myasthenia gravis (gMG) is a **rare autoimmune disorder** characterized by loss of muscle function and severe muscle weakness.[1]





The **neuromuscular junction (NMJ)** is the connection point between **nerve cells** and the **muscles** they control.[1]



80% of people with gMG are AChR+, meaning they produce specific antibodies (anti-AChR) that bind to signal receptors at the NMJ. This binding activates the complement system, causing the immune system to attack the NMJ. This leads to inflammation and a **breakdown in communication** between the **brain** and the **muscles**.[1-4]

Diagnosed prevalence of gMG in adults

~90K[5] ~89K[5] ~24K[6]

Most commonly begins for **women before the age of 40** and for **men after the age of 60.**[7-9]

Initial symptoms may include[10,11]

- **Slurred speech**
- **Double vision**
- **Droopy eyelids**
- **Lack of balance**

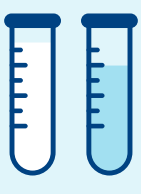
which can often lead to more severe symptoms as the disease progresses[10,11]

- **Impaired swallowing**
- **Choking**
- **Extreme fatigue**
- **Respiratory failure**

HOW IS gMG DIAGNOSED?[10]

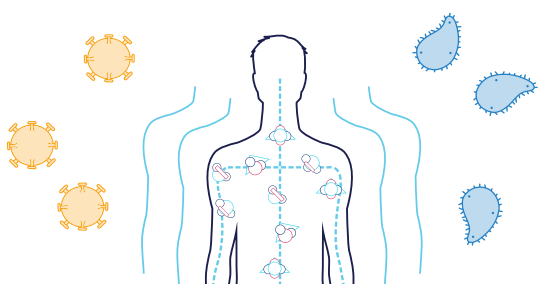
gMG is typically diagnosed with a **physical examination** to evaluate muscle function.

Blood tests for certain antibodies, including anti-acetylcholine receptor (anti-AChR), are also used

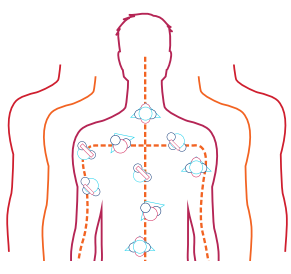


as well as **nerve and muscle stimulation** and **chest computed tomography** or **magnetic resonance imaging (MRI)**.

THE COMPLEMENT SYSTEM



The complement system is a part of the immune system and is **essential to the body's defense against infection**.[12]



When the system is **thrown out of balance**, or dysregulated, these proteins can **trigger a dangerous, uncontrolled cascade of reactions** that attack cells and tissues resulting in **harmful inflammation** and the **destruction of healthy cells**.[13]

WHAT ROLE DOES COMPLEMENT INHIBITION PLAY IN TREATING gMG?

Alexion's clinical studies in gMG have shown that **inhibiting the complement system** (by blocking the C5 protein) prevents the body's attack on the NMJ.

This **reduces the damage** and helps prevent the breakdown in communication between the brain and the muscles.

Alexion's leadership in complement inhibition has set the course for the continued study and development of innovative treatments for certain rare complement-mediated neurological diseases, including gMG.

WHAT TREATMENT APPROACH IS BEING STUDIED BY ALEXION?

In addition to **our development of therapies that are approved for adults with gMG who are AChR antibody positive**, we continue to advance research and other clinical trial programs in the disease.

We remain focused on **accelerating the discovery and development of new**, **life-changing therapies** for people living with gMG.

References:

1. Anil, R., Kumar, A., Alaparthi, S., Sharma, A., Nye, JL., Roy, B., O'Connor, KC., Nowak, R., (2020). Exploring outcomes and characteristics of myasthenia gravis: Rationale, aims and design of registry - The EXPLORE-MG registry. *J Neurol Sci.* 2020 Jul 15;414:116830.
2. Oh SJ., (2009). Muscle-specific receptor tyrosine kinase antibody positive myasthenia gravis current status. *Journal of Clinical Neurology*. 2009b Jun 1;5(2):53-64.
3. Tomschik, M., Hilger, E., Rath, J., Mayer, EM., Fahrner, M., Cetin, H., Löscher, W., Zimprich, F., (2020). Subgroup stratification and outcome in recently diagnosed generalized myasthenia gravis. *Neurology*. 2020 Sep 8;95(10):e1426-e1436.
4. Hendricks, TM., Bhatti, MT., Hodge, D., Chen, J., (2019). Incidence, Epidemiology, and Transformation of Ocular Myasthenia Gravis: A Population-Based Study. *Am J Ophthalmol*. 2019 Sep;205:99-105.
5. Westerberg, E., Punga, A., (2020). Epidemiology of Myasthenia Gravis in Sweden 2006–2016. *Brain and behavior*. 2020 Nov;10(11):e01819.
6. Lai, CH., Tseng, HK., (2010). Nationwide Population-Based Epidemiological Study of Myasthenia Gravis in Taiwan. *Neuroepidemiology*. 2010 June;35:66-71.
7. *Myasthenia Gravis*. National Organization for Rare Disorders (NORD). Retrieved July 29, 2021, from https://rarediseases.org/rare-diseases/myasthenia-gravis/.
8. Howard, J. F. (2015). *Clinical Overview of MG*. Retrieved July 29, 2021, from https://myasthenia.org/Professionals/Clinical-Overview-of-MG.
9. Sanders, D. B., Raja, S. M., Guptill J. T., Hobson-Webb, L. D., Juel, V. C., & Massey, J. M. (2020). The Duke myasthenia gravis clinic registry: I. Description and demographics. *Muscle & Nerve, 63*(2), 209-216. https://doi.org/10.1002/mus.27120
10. *Myasthenia Gravis Fact Sheet*. (2020, April 27). National Institutes of Neurological Disorders and Stroke. Retrieved July 28, 2021, from https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Myasthenia-Gravis-Fact-Sheet.
11. Ding J., Zhao, S., Ren, K., Dang, D., Li, H., Wu, F., Zhang, M., Li, Z., & Guo, J. (2020). Prediction of generalization of ocular myasthenia gravis under immunosuppressive therapy in Northwest China. *BMC Neurology, 20*(238). https://doi.org/10.1186/s12883-020-01805-1
12. Merle, N. S., Church, S. E., Fremeaux-Bacchi, V., & Roumenina, L. T. (2015). Complement system part I – molecular mechanisms of activation and regulation. *Frontiers of Immunology*, 6:262. https://doi.org/10.3389/fimmu.2015.00262
13. Merle, N. S., Noe, R., Halbwachs-Mecarelli, L., Fremeaux-Bacchi, V., & Roumenina, L. T. (2015). Complement system part II: role in immunity. *Frontiers of Immunology*, 6:257. https://doi.org/10.3389/fimmu.2015.00257

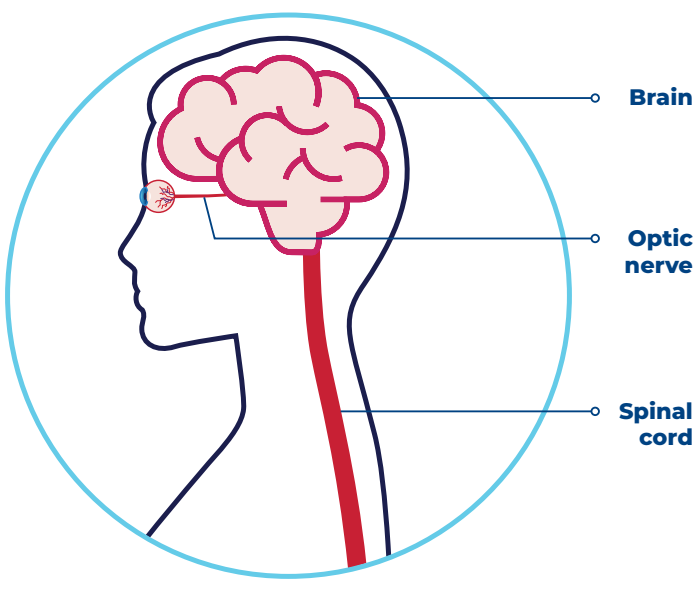
Neuromyelitis Optica Spectrum Disorder (NMOSD)

ALEXION
AstraZeneca Rare Disease

WHAT IS NEUROMYELITIS OPTICA SPECTRUM DISORDER?

NMOSD is a **rare disease** in which the immune system is inappropriately activated to target healthy tissues and cells in the central nervous system (CNS).[1]

Approximately three-quarters of people with NMOSD are anti-AQP4 antibody-positive, meaning they produce antibodies that bind to a specific protein, aquaporin-4 (AQP4). This binding can inappropriately activate the complement system to **destroy cells** in the **optic nerve**, **spinal cord**, and **brain**.[2,3]



Diagnosed prevalence in adults is[4,5]

~7.5K ~6K ~4K

NMOSD most commonly **affects women** and begins in the **mid-30s**. **Men and children** may also develop NMOSD, but it is even more rare.[6–9]

Patients with NMOSD may experience[10]

- **Vision problems**
- **Intense pain**
- **Loss of bladder/ bowel function**
- **Abnormal skin sensations (e.g., tingling, prickling or sensitivity to heat/cold)**
- **Impact on coordination and/or movement**

Most people living with NMOSD experience **unpredictable attacks, known as relapses**. Each relapse can result in cumulative disability including **vision loss**, **paralysis**, and sometimes, **premature death**.[11,12]

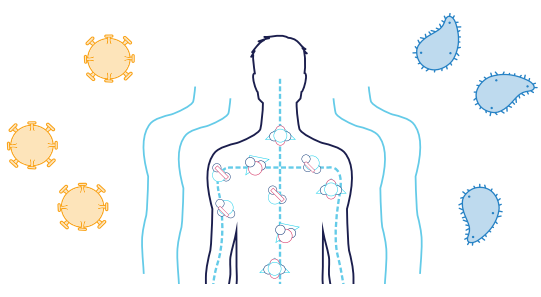
HOW IS NMOSD DIAGNOSED?

The journey to diagnosis can be long, with the disease **sometimes misdiagnosed**. NMOSD is a **distinct disease from other CNS diseases**, including multiple sclerosis (MS).[1,13]

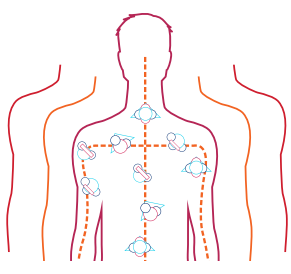
A **neurologist or neuro-ophthalmologist** diagnoses NMOSD by one or more of the following:[1,7]

- ☑ **Evidence of a blood test for the NMOSD-specific biomarker**
- ☑ **At least 1-2 core manifestations of the disease (e.g., inflammation of the optic nerve or spinal cord)**
- ☑ **Magnetic resonance imaging (MRI) of the brain, spinal cord or optic nerve**
- ☑ **Identification of certain patterns in how the disease presents (such as length and location of the lesions caused by tissue damage)**

THE COMPLEMENT SYSTEM



The complement system is a part of the immune system and is **essential to the body's defense against infection**.[14]



When the system is **thrown out of balance**, or dysregulated, these proteins can **trigger a dangerous, uncontrolled cascade of reactions** that attack cells and tissues resulting in **harmful inflammation** and the **destruction of healthy cells**.[15]

WHAT ROLE DOES COMPLEMENT INHIBITION PLAY IN TREATING NMOSD?

Alexion's clinical studies in NMOSD have shown that **inhibiting the complement system** (by blocking the C5 protein) **reduces the risk of relapses.**

Alexion's leadership in complement inhibition has set the course for the continued study and development of innovative treatments for certain rare complement-mediated neurological diseases, including NMOSD.

WHAT TREATMENT APPROACH IS BEING STUDIED BY ALEXION?

In addition to **developing the first approved therapy for adults with anti-AQP4 antibody-positive NMOSD**, we continue to advance research and other clinical trial programs in the disease, including an ongoing **Phase 3 study involving our long-acting complement inhibitor**.

We remain focused on **accelerating the discovery and development of new, life-changing therapies** for people living with NMOSD.

References:

1. Jarius, S., Wildemann, B. (2013). The History of Neuromyelitis Optica. *J Neuroinflammation* 10, 797.
2. Hamid SHM., et al. (2017, Oct.) What Proportion of AQP4-IgG-negative NMO Spectrum Disorder Patients are MOG-IgG Positive? A Cross Sectional Study of 132 Patients. *J Neurol*., 264(10):2088-2094.
3. Wingerchuk, D. M., et al. (2017). Neuromyelitis Spectrum Disorders. *Mayo Clinic proceedings*, 92(4), 663–679.
4. Cossburn, M., et al. (2012). The Prevalence of Neuromyelitis Optica in South East Wales." *Eur J Neurol*., 19(4): 655-659.
5. Miyamoto K., et al. (2018). Nationwide Epidemiological Study of Neuromyelitis Optica in Japan. *J Neurol Neurosurg Psychiatry*, 89(6):667-68.
6. Bukhari W., et al. (2017). Incidence and Prevalence of NMOSD in Australia and New Zealand. *J Neurol Neurosurg Psychiatry*., 88(8):632-8.
7. Wingerchuk, D. M., et al. (2006). Revised diagnostic criteria for neuromyelitis optica. *Neurology, 66*(10), 1485–1489.
8. Drori, T., et al. (2014). Diagnosis and classification of neuromyelitis optica (Devic's syndrome). *Autoimmunity reviews, 13*(4-5), 531–533.
9. Eaneff, S., et al. (2017). Patient perspectives on neuromyelitis optica spectrum disorders: Data from the PatientsLikeMe online community. *Multiple sclerosis and related disorders, 17*, 116–122.
10. Mutch K, et al. (2014). Life on Hold: The Experience of Living with Neuromyelitis Optica. *Disabil Rehabil*.,36(13):1100-7.
11. Kessler, R. A., et al. (2016). Treatment of Neuromyelitis Optica Spectrum Disorder: Acute, Preventive, and Symptomatic. *Current treatment options in neurology, 18*(1), 2.
12. Jiao, Y., et al. (2013). Updated Estimate of AQP4-IgG Serostatus and Disability Outcome in Neuromyelitis Optica. *Neurology, 81*(14), 1197–1204.
13. Mealy, M. A., et al. (2019). Assessment of Patients with Neuromyelitis Optica Spectrum Disorder Using the EQ-5D. *International journal of MS care, 21*(3), 129–134.
14. Merle, N. S., et al. (2015). Complement System Part II: Role in immunity. *Frontiers of Immunology*, 6:257.
15. Garred, P., Tenner, A. J., & Mollnes, T. E. (2021). Therapeutic Targeting of the Complement System: From Rare Diseases to Pandemics. *Pharmacological Reviews, 73*(2) 792-827.

HYPOPHOSPHATASIA (HPP)

ALEXION®
AstraZeneca Rare Disease

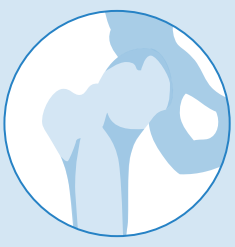
WHAT IS HYPOPHOSPHATASIA?

Hypophosphatasia (HPP) is a **rare, genetic (inherited), metabolic disease** characterized by **impaired mineralization ("calcification")**, the process that hardens and strengthens bones and teeth.[1,2]

This can lead to poor growth and development, weakness and deformity of bones and other skeletal abnormalities, and premature loss of teeth with the root intact. **As a result, the disease can have a debilitating impact, including loss of physical function.**[1,3]

HPP is caused by a defect in the gene that is responsible for making an enzyme known as **alkaline phosphatase (ALP)**, which is important for building healthy bones.[1,4]

HEALTHY BONE



When ALP functions normally, it allows calcium and phosphate to bind together to **form healthy, strong bones**.[4,5]

BONE IMPACTED BY HPP

In people with HPP, ALP levels are low, which can **prevent proper bone development** and can **cause calcium and phosphate to build up in other places throughout the body, damaging organs.**[3]

The severity of HPP can be wide-ranging and may present in many different ways.

HPP can **affect males and females of all ages.**[1]

When signs and symptoms are present **before 6 months of age**, HPP is referred to as **perinatal/infantile-onset and can be fatal.**[1]

All patients, including those whose signs or symptoms are not recognized until childhood or adulthood, may experience **significant disease burden that impacts their daily life**, including the ability to perform daily tasks or walk.[1]

SIGNS AND SYMPTOMS MAY VARY AND CAN IMPACT MANY DIFFERENT PARTS OF THE BODY, INCLUDING:[1,2,6-9]

Bones
(abnormally shaped head*, bone deformities, frequent fractures, persistent bone pain)

Muscles and joints
(muscle weakness, fatigue, arthritis)

Ribs and lungs
(underdeveloped ribs and lungs*, severe breathing difficulties*)

Central nervous system
(Vision loss, seizures*)

Kidneys
(kidney stones, decreased kidney function)

Teeth
(early tooth loss with the root intact, gum disease)

New symptoms can appear at **any age and worsen over time**, causing significant **disability or life-threatening complications**.

*Symptoms normally seen in infants and/or young children

HOW IS HPP DIAGNOSED?

Since HPP shares symptoms with other, more common diseases, **it can be misdiagnosed, and diagnosis is often delayed.**[1, 10]

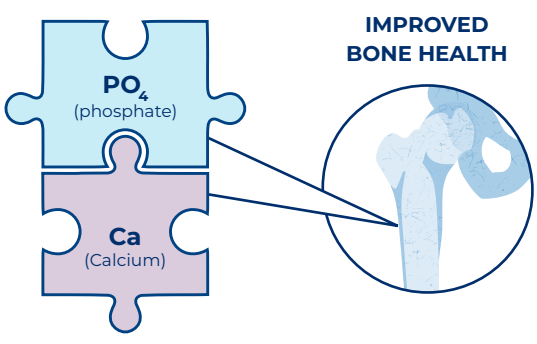
Once a person shows signs and symptoms of HPP, **a full clinical assessment and blood test** for low ALP can help lead to a correct diagnosis. **Genetic testing** may also be helpful in confirming HPP.[11]

HPP is a lifelong disease, so an **early diagnosis is critical** to ensure appropriate disease management.[11]

HOW HAS HPP TREATMENT EVOLVED?

Initially, treatment for HPP relied only on supportive care and symptom management, but research has led to more options.

Clinical studies in HPP have shown that replacing deficient ALP can improve the body's ability to mineralize bone by allowing **phosphate and calcium to bind together**. This has proven **to improve bone health and mobility, as well as survival in infants.**[12]



Alexion's leadership in rare disease led to the **first and only approved medicine** to treat the underlying cause of HPP for patients with **signs and symptoms of the disease during childhood.**

HOW IS ALEXION CONTINUING TO INNOVATE FOR HPP PATIENTS?

We continue to **innovate for patients with HPP and accelerate the development of life-changing therapies.**

Alexion is progressing our next generation alkaline phosphatase enzyme replacement therapy in clinical trials in adults and children with HPP, with the intention of **uncovering new ways to improve the patient experience and provide additional treatment options** to help more people living with this devastating disease.

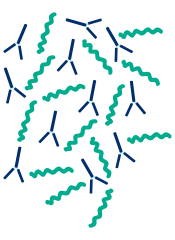
References:

1. Rockman-Greenberg C. (2013). Hypophosphatasia. *Pediatric endocrinology reviews: PER, 10 Suppl 2*, 380–388.
2. FRASER D. (1957). Hypophosphatasia. *The American journal of medicine, 22*(5), 730–746.
3. Beck C, et al. (2009). Hypophosphatasia —recent advances in diagnosis and treatment. *The Open Bone Journal*; 1:8-15.
4. Whyte MP. (2008) Hypophosphatasia: nature's window on alkaline phosphatase function in humans. *Principles of Bone Biology, Academic Press*; 2008:1573-1598.
5. Whyte M. P. (2010). Physiological role of alkaline phosphatase explored in hypophosphatasia. *Annals of the New York Academy of Sciences*, 1192, 190–200.
6. Whyte MP, et al. (2019). Natural History of Perinatal and Infantile Hypophosphatasia: A Retrospective Study. *The Journal of Pediatrics*. 209, 116–124.e4.
7. Weber TJ, et al. (2016). Burden of disease in adult patients with hypophosphatasia: Results from two patient-reported surveys. *Metabolism: clinical and experimental, 65*(10), 1522–1530.
8. Beck C, et al. (2011). Whole-body MRI in the childhood form of hypophosphatasia. *Rheumatology international*, 31(10), 1315–1320.
9. Leung EC, et al. (2013). Outcome of perinatal hypophosphatasia in manitoba mennonites: a retrospective cohort analysis. *JIMD reports*, 11, 73–78.
10. Mohn A, et al. (2011). Hypophosphatasia in a child with widened anterior fontanelle: lessons learned from late diagnosis and incorrect treatment. *Acta paediatrica* (Oslo, Norway: 1992), 100(7), e43–e46.
11. Mornet, E., & Nunes, M. E. (2016). Hypophosphatasia. *GeneReviews®. University of Washington, Seattle*.
12. Magdaleno AL, et al (2019). ADULT-ONSET HYPOPHOSPHATASIA: BEFORE AND AFTER TREATMENT WITH ASFOTASE ALFA. *AACE clinical case reports, 5*(6), e344–e348.

AL Amyloidosis

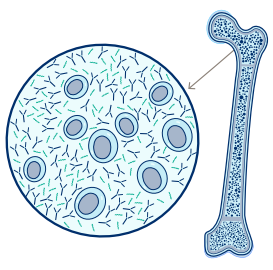
ALEXION®
AstraZeneca Rare Disease

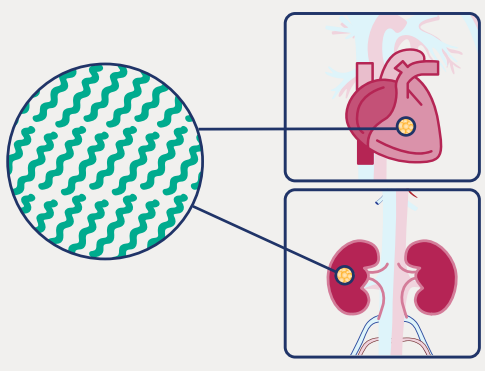
WHAT IS AL AMYLOIDOSIS?



Amyloidosis is a **group of rare diseases** caused by **abnormal proteins that misfold and clump together to form toxic amyloids,** and deposit in tissues or organs.[1]

One type is amyloid light chain, or AL, amyloidosis **where proteins that function as antibodies, also known as immunoglobulins, are produced abnormally by defective plasma cells in the bone marrow.**[1]





Amyloid can buildup in many organs, particularly in the heart and kidneys, which can result in **significant organ damage and organ failure that can ultimately be fatal.**[2]

SYMPTOMS MAY INCLUDE:[3]

Swollen arms and legs

Extreme shortness of breath

Abnormal heartbeat

Nausea

Diarrhea

Numbness or tingling in extremities

Enlarged tongue

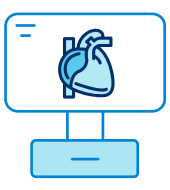
Rash around eyes

and many other **vague symptoms that mimic other diseases** that often complicate diagnosis.[2]

HOW IS AL AMYLOIDOSIS DIAGNOSED?

Diagnosis of AL amyloidosis can be relatively straightforward, but is often delayed and can take **>6 months after symptoms begin.**[4]

Once suspected, blood and urine tests are conducted first, followed by a tissue biopsy to confirm amyloidosis.[5]

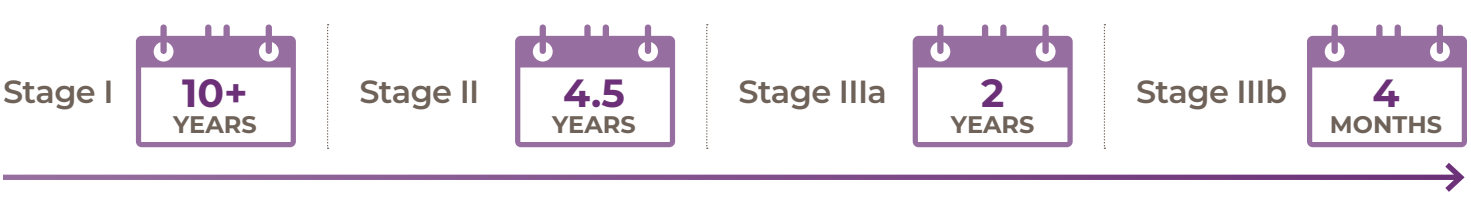


Imaging of the impacted organs can help determine the severity of the condition.[5]

CARDIAC STAGING AND PROGNOSIS

Stage of disease and prognosis mainly depend on the **extent of cardiac involvement and are based on blood tests.**[1]

Median Overall Survival:[5*]



**Based on the 2013 European Modification of the 2004 Standard Mayo Clinic Staging*

Rapid, accurate diagnosis leading to initiation of treatment is essential to mitigate the impact of this disease on **survival and quality of life.**[2]

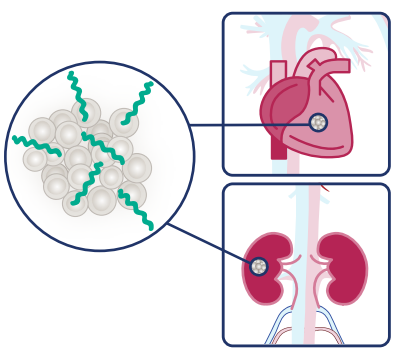
WHAT ARE CURRENT TREATMENT NEEDS?

There are no approved treatments that address the significant organ damage caused by the disease. Current treatments, including **bone marrow transplantation and/or chemotherapy,** focus on preventing and/or suppressing the formation of new toxic amyloids.[1]

As a result, the disease and organ damage may continue to progress and ultimately lead to organ failure and death.[1,6]

WHAT TREATMENT APPROACH IS BEING STUDIED BY ALEXION?

Alexion is advancing the **first potential treatment to address the devastating organ damage caused by AL amyloidosis.**



CAEL-101 is a novel, investigational, **first-in-class therapy** designed to recognize, bind to and remove existing amyloid deposits from organs and thereby improve and/or restore functionality of damaged organs, enhance quality of life and ultimately improve survival.

CARDIAC AMYLOID REACHING FOR EXTENDED SURVIVAL (CARES) CLINICAL TRIAL PROGRAM IN AL AMYLOIDOSIS[7,8]

TRIAL DESIGN

Two parallel, double-blind, randomized **Phase 3 studies** are being conducted to evaluate the efficacy and safety of CAEL-101 combined with current treatments for AL amyloidosis. These studies include patients who are newly diagnosed and have not yet started treatment.

ENROLLMENT

~260 patients with Mayo stage IIIa disease

~110 patients with Mayo stage IIIb disease

70+ study locations across North America, the United Kingdom, Europe, Israel, Japan, and Australia

PRIMARY ENDPOINTS

- Overall survival
- Safety and tolerability

SECONDARY ENDPOINTS

- Improvement in the six-minute walk test
- Quality of life measures
- Improvement in cardiac function

CAEL-101 has received Orphan Drug Designation for the treatment of AL amyloidosis in the U.S. and EU

CAEL-101 is not approved for the treatment of AL amyloidosis. The safety and efficacy of CAEL-101 for the treatment of AL amyloidosis is currently being studied.

References:

1. Desport, E., Bridoux, F., Sirac, C. et al. AL Amyloidosis. Orphanet J Rare Dis 7, 54 (2012).
2. Sanchorawala, V. Light-Chain (AL) Amyloidosis: Diagnosis and Treatment. *Clin J Am Soc Nephrol 1*: 1331–1341, 2006.
3. Amyloidosis - Symptoms and causes. (2020, March 14). Mayo Clinic. Accessed at: https://www.mayoclinic.org/diseases-conditions/amyloidosis/symptoms-causes/syc-20353178. Accessed March 2021.
4. Lousada, I., Comenzo,. Landau, H., Guthrie, S., Merlini, G. Light Chain Amyloidosis: Patient Experience Survey from the Amyloidosis Research Consortium. *Adv Ther* (2015) 32:920–928.
5. Dittrich T., Kimmich C., Hegenbart U., Schönland S., O. Prognosis and Staging of AL Amyloidosis. *Acta Haematol* 2020;143:388-400.
6. Grogan, M., Dispenzieri, A., Gertz, M. Light-chain cardiac amyloidosis: strategies to promote early diagnosis and cardiac response. Heart 2017;103:1065–1072.
7. NIH, U.S. National Library of Medicine. A Study to Evaluate the Effectiveness and Safety of CAEL-101 in Patients With Mayo Stage IIIb AL Amyloidosis. Accessed at: https://www.clinicaltrials.gov/ct2/show/NCT04504825?term=Caelum&cond=AL+Amyloidosis&draw=2&rank=2. Accessed March 2021.
8. NIH, U.S. National Library of Medicine. A Study to Evaluate the Effectiveness and Safety of CAEL-101 in Patients With Mayo Stage IIIa AL Amyloidosis. Accessed at: https://www.clinicaltrials.gov/ct2/show/NCT04512235?term=Caelum&cond=AL+Amyloidosis&draw=2&rank=1. Accessed March 2021.

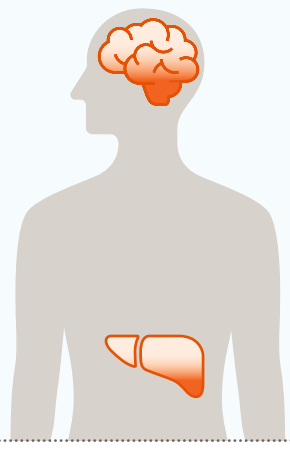
Wilson Disease

AstraZeneca Rare Disease

What is Wilson disease?

Wilson disease is a **rare and progressive genetic (inherited) condition** in which the body's **pathway for removing excess copper is compromised**.[1]

Over time, that results in the **build-up of toxic copper levels** in the liver, brain and other organs leading to damage that greatly impacts a patient's life.[1]



Diagnosed prevalence is

~5K **~5K** **~2.5K**

but prevalence is believed to be higher.[2]

29 Cu COPPER

Copper is an important nutrient that is **not produced by the body**, but **absorbed from a person's diet** and only required in small amounts.[3]

Patients can develop a wide range of symptoms, including **liver disease** and/or **psychiatric or neurological symptoms**, such as:

- **personality changes** (such as depression, anxiety and phobias)
- **tremors**
- **difficulty walking**
- **difficulty swallowing**
- **difficulty talking**
- **changes to the cornea**

In some cases, **the damage and loss of function may be irreversible**.[1,4,5]

How is Wilson disease diagnosed?

blood tests · liver biopsy · eye exam · urine test · genetic testing

Diagnosis typically requires a combination of **5+ tests**, scoring system of **7 different signs and symptoms** and/or invasive procedures like a liver biopsy.[5]

Although the disease is present at birth, the average age of diagnosis is **5-35 years.**[4,5]

People living with Wilson disease frequently face two to three years of misdiagnoses.[6]

2–3 years

Early, improved diagnosis is key to enable earlier treatment and **help reduce the risk of worsening organ damage**.[5,7]

What are the current treatment needs?

Existing standard-of-care treatments either remove copper from the blood or limit copper absorption in the digestive system.[4,5] However, even after treatment is initiated, some patients experience **worsening of disease, especially of neurologic symptoms**.[4,5]

These treatments can be **difficult to tolerate** and have **challenging dosing schedules.**[8,9]

What treatment approach is being studied by Alexion?

Alexion is advancing the **first potential new innovation in treating Wilson disease in more than 30 years.**[10]

ALXN1840 is designed to be the **first targeted de-coppering therapy** that **selectively and tightly binds to and removes copper** from the body's tissues and blood.

This once-daily, oral medicine has the **potential to change the disease trajectory** and what it means to live with Wilson disease.[11]

ALXN1840 is not approved for the treatment of Wilson disease. The safety and efficacy of ALXN1840 for the treatment of Wilson disease is currently being studied.

References:

1. Patil, M., et al. (2013) *J Clin Exp Hepatol*, 3, 321-336.
2. Alexion: Wilson's Disease: Epidemiology Findings (2018, March). Forecast of Diagnosed Prevalent Cases (Ages 5+) for 7 Major Markets (US, EU5, Japan). 5-6.
3. NIH, Office of Dietary Supplements. (2020, June 3). Copper Factsheet for Health Professionals. Accessed at: https://ods.od.nih.gov/factsheets/Copper-HealthProfessional/. Accessed February 2021.
4. Roberts, E.A., Schilsky, M.L. American Association for the Study of Liver D. (2008). Diagnosis and treatment of Wilson disease: An update. *Hepatology*, 47(6), 2089-2111.
5. European Association for the Study of the Liver. (2012). EASL clinical practice guidelines: Wilson's disease. *J Hepatol*, 56(3), 671-685.
6. Poujois, A., Woimant, F. (2019). Challenges in the diagnosis of Wilson disease. *Ann Transl Med*, 7, S67.
7. Poujois, A., Woimant, F., Samson, S., et al. (2018). Characteristics and prevalence of Wilson's disease: A 2013 observational population-based study in France. *Clin Res Hepatol Gastroenterol*, 42, 57–63.
8. Schilsky, M.L. (2017). Wilson disease: Diagnosis, treatment, and follow-up. *Clin Liver Dis*, 21, 755–67.
9. Litwin, T., Dziezyc, K., Czlonkowska, A. (2019). Wilson disease-treatment perspectives. *Ann Transl Med*, 7, S68.
10. Kathawala, M., Hirschfield, G. M. (2017, November). Insights into the management of Wilson's disease. *Therap Adv Gastroenterol*, 889-905. Doi: 10.1177/1756283X17731520.
11. NIH, U.S. National Library of Medicine. Efficacy and safety of ALXN1840 (formerly named WTX101) administered for 48 weeks versus standard of care in patients with Wilson disease with an extension period of up to 60 months. Accessed at: https://clinicaltrials.gov/ct2/show/NCT03403205. Accessed February 2021.