



## Prilenia Announces Publication of Data Elucidating a Mechanism for Neuroprotective Potential of Pridopidine

- This new research adds to the growing understanding of pridopidine as a highly selective S1R agonist that has shown neuroprotective properties in multiple models –*
- Research details the role of pridopidine’s mechanism of action in autophagy, a cellular process critical to preserving neuronal health –*
- By improving autophagy, pridopidine may reduce the toxic protein aggregation that is a hallmark of neurodegenerative diseases –*

NAARDEN, NL, 25 May 2022 --- [Prilenia Therapeutics B.V.](#), a clinical stage biotechnology company focused on the urgent mission to develop novel therapeutics to slow the progression of neurodegenerative and neurodevelopmental disorders, today announced publication of its research in the peer-reviewed journal *Autophagy* which support pridopidine’s potential neuroprotective properties by enhancing autophagy in an amyotrophic lateral sclerosis (ALS) model.

Pridopidine is an oral, highly selective and potent Sigma-1 Receptor (S1R) agonist currently in late-stage development for the potential treatment for Huntington’s disease (HD) and ALS. In clinical studies to date, pridopidine (45mg twice daily) has exhibited a safety and tolerability profile similar to placebo (Geva, 2022).

The S1R is highly expressed in the brain and spinal cord where it regulates several processes that are commonly impaired in various neurodegenerative diseases. Activation of the S1R by pridopidine stimulates multiple cellular pathways, including autophagy, which are essential to neuronal function and survival, and may lead to neuroprotective effects (Maurice, 2021).

Autophagy is the process by which a cell eliminates old or damaged proteins (Fleming et al., 2022). By improving autophagy, pridopidine may reduce the toxic protein aggregation that is a hallmark of neurodegenerative diseases such as HD, ALS, Alzheimer’s disease and Parkinson’s disease.

Shuttling of molecules from the cytoplasm to the nucleus (nucleocytoplasmic shuttling), via the nucleopore complex is essential for neuronal function and survival. A critical step in autophagy is the transport of the Transcription Factor EB (TFEB) into the nucleus, where it upregulates expression of autophagy-related genes (Cunningham et al., 2020). This nucleocytoplasmic process is impaired in various neurodegenerative diseases, including ALS (Coyne et al., 2020).

“This study confirms that pridopidine plays an important role in maintaining the health of a neuronal cell by activating the S1R which in turn interacts with specific proteins to initiate the autophagic process,” said Tsung-Ping Su, Ph.D., Chief, Cellular Pathobiology Section, National Institute on Drug Abuse (NIDA) located in Baltimore, MD. “While this paper focuses primarily on an ALS model, our results also suggest promise for a pharmacological approach targeting S1R across diverse diseases in which autophagy is impaired.”

Highlights from the article entitled, "[Nucleoporin POM121 signals TFEB-mediated autophagy via activation of SIGMAR1/sigma-1 receptor chaperone by pridopidine](#)" include:

- This new research shows that pridopidine activates the S1R by facilitating its disassociation from the ER protein BiP, freeing the S1R to interact with other protein partners.
- The activated S1R stabilizes the nucleopore complex by interacting with POM121 (a central nucleopore protein), facilitating the translocation of TFEB into the nucleus.
- TFEB translocation into the nucleus initiates the autophagic process by upregulating the expression of autophagy genes, leading to neuroprotection.

G4C2 repeats within the c9orf72 gene are the most common cause of familial ALS (fALS)(DeJesus-Hernandez et al., 2011). This study utilized a cell model of motor neurons over expressing G4C2 repeats that destabilizes the nucleopore and reduces the nucleocytoplasmic transport of TFEB, leading to impaired autophagy and neurodegeneration. In this model, pridopidine activation of the S1R rescues TFEB shuttling and upregulates autophagy, leading to neuroprotection.

"Our collaborations with leading researchers as well as our close working relationships within the HD and ALS communities are important as we enhance our understanding of the mechanism of action of pridopidine and its impact on neurodegenerative conditions," said Dr. Michael R. Hayden, CEO and Founder of Prilenia. "The data published in *Autophagy* reinforce findings from earlier studies indicating that pridopidine may offer neuroprotective effects. We look forward to sharing additional information about pridopidine as data from our late-stage clinical studies become available."

This new research adds to the growing understanding of pridopidine's mechanism of action as a highly selective S1R agonist, which was previously shown to improve cellular functions impaired in neurodegenerative disease such as mitochondrial function, ER stress, energy production, trophic factor availability and synaptic plasticity (Geva et al., 2016; Naia et al., 2021; Ryskamp et al., 2017; Smith-Dijak et al., 2019).

## About Pridopidine

Pridopidine (45mg twice daily) is an oral, highly selective Sigma-1 Receptor agonist that has exhibited a safety and tolerability profile similar to placebo in clinical studies to date.

Pridopidine is currently being assessed as a potential treatment for people living with Huntington's disease in PROOF-HD, a global Phase 3 clinical trial. [The study, which includes 59 sites and 499 participants, completed enrollment ahead of schedule and with numbers over the enrollment target in late 2021.](#) Prilenia recently received Fast Track designation for pridopidine for the treatment of HD.

In addition to PROOF-HD, pridopidine is being evaluated as a potential treatment for people living with ALS in the HEALEY ALS Platform Trial. This study represents the first of its kind in ALS and is designed to accelerate the development of promising new treatments. [The study was fully enrolled in early 2022, ahead of schedule, and includes 163 participants across 52 sites.](#) Pridopidine has received Orphan Drug Designation for ALS in the U.S. and Europe.

## About Prilenia

Prilenia is a clinical stage biotech startup founded in 2018 focused on the urgent mission to develop novel therapeutics to slow the progression of neurodegenerative diseases and neurodevelopmental disorders. Prilenia is backed by a group of well-respected investors including: Forbion, Morningside, Sands Capital, SV Health Investors, Sectoral Asset Management, Talisman, Amplitude Ventures and the ALS Investment Fund. The Company is based in Naarden, the Netherlands, Herzliya, Israel and Boston, MA in the U.S.

For more information visit [www.prilenia.com](http://www.prilenia.com) and follow us on [LinkedIn](#) and [Twitter](#).

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