Health Technology Briefing
May 2024

Pridopidine for treating Huntington's disease in adults

Company/Developer	Prilenia

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30533	NICE ID: Not Available	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pridopidine is in clinical development for the treatment of adult patients with Huntington's disease (HD). HD is a hereditary neurodegenerative disorder (disease of the nervous system) caused by a genetic mutation in the Huntingtin gene (*HTT*) that leads to the progressive loss of nerve cells in the brain. This results in movement dysfunction, cognitive decline, and neuropsychiatric or behavioural symptoms. HD usually presents in mid-adulthood and progressively worsens over time. Currently, there is no cure for HD, and approved treatments only help to manage chorea symptoms (unpredictable muscle movements), with no benefits on other symptoms including function, cognition, behavioural and non-chorea motor symptoms.

Pridopidine is a new chemical entity taken orally that selectively activates the sigma-1 receptor (S1R) in the brain. S1R is widely expressed in the brain where it regulates several mechanisms commonly impaired in neurodegenerative diseases such as HD. Pridopidine activates the S1R, helping clear toxic proteins, boost energy production, and reduce cellular stress and inflammation, resulting in neuroprotection (preservation of neuronal structure and function). There are currently no treatment options to slow the progression of HD therefore if licensed, pridopidine would be the first to do so.

Proposed Indication

Treatment of adult patients with Huntington's disease (HD).[1]

Technology

Description

Pridopidine (PL-101, formerly TV-7820 and ACR16) is a first-in-class selective and potent sigma-1 receptor (S1R) agonist.[2-4] The S1R is broadly expressed in the brain and central nervous system, particularly in the spinal cord, brain stem, basal ganglia and cortex, where it regulates several cellular mechanisms commonly impaired in neurodegenerative diseases such as HD.[5] By activating the S1R, pridopidine enhances multiple cellular pathways, including the clearance of toxic proteins, an increase in energy production, and a reduction in cellular stress and inflammation, resulting in neuroprotection.[2,5]

Pridopidine is currently in clinical development for the treatment of patients with HD. In the double-blind period of the phase III clinical trial (PROOF-HD, NCT04556656, EudraCT-2020-002822-10), participants were given 45 mg pridopidine, orally, twice daily for 65-78 weeks.[1,2,6]

Key Innovation

Currently there are no effective medicinal products that modify HD progression. Currently, approved therapies focus on the treatment of chorea symptoms.[1,7-9] In the PRIDE-HD trial, pridopidine 45 mg twice daily was associated with maintenance of functional capacity (measured by total functional capacity (TFC)) compared to placebo at 52 weeks.[1,7] Furthermore, this benefit was maintained long term up to additional five years when participants were followed during an open-label study.[10]

If licensed, pridopidine will provide the first treatment option to modify disease progression for patients with HD, who currently have no effective therapies available.

Regulatory & Development Status

Pridopidine does not currently have marketing authorisation in the EU/UK for any indication.

Pridopidine has also completed phase II clinical development for:[11]

- Amyotrophic lateral sclerosis

Pridopidine has the following regulatory designations/awards:

- An orphan drug in the EU in 2023 for HD[12]
- Fast Track designation by the US FDA for HD in November 2021[13]

Patient Group

Disease Area and Clinical Need

HD is a chronic progressive, ultimately fatal autosomal inherited condition caused by a mutation in the Huntingtin gene (*HTT*) that causes parts of the brain to stop working properly over time.[7,14] In HD, there is progressive neuronal loss in the striatum. This loss is believed to be caused by the dysregulation of the endoplasmic reticulum, altered mitochondrial function, reduced autophagy, and increased endoplasmic reticulum stress, all ultimately leading to accelerated neuronal death.[7] This type of neurodegenerative disease causes an irreversible decline in daily function, mood, behaviour, and cognitive decline, as well as abnormal movement and motor impairment. The disease is universally fatal after a period up to 20 years.[14] The mutant Huntingtin gene is inherited in an autosomal dominant pattern, such that each child of an

affected parent has a 50% risk of inheriting the condition.[7] Symptoms of HD usually become apparent between the ages of 30 to 50, though very rare cases of children as young as two years old and adults in their eighties may also develop symptoms. Most individuals in the late stages of illness require enormous assistance and become completely dependent on others. They lose the ability to walk, talk, and feed themselves, but are still conscious, aware and know themselves and their families.[14,15]

There are at least 7000 people living with HD in the UK.[16] A UK study found that individuals with HD were at an approximately 4 times increased risk of death compared with the general population. The most common underlying cause of death was HD, demonstrating the fatal effects of the disease.[17] Another UK study conducted from 2000 to 2018 inclusively, concluded a prevalence of 8.2 cases per 100,000 people (95% CI (7.7-8.8)), whereby prevalence was similar in males and females. The same study also found that in 2018, the incidence of HD was 0.8 (0.5–1.19) per 100000.[17] In England, during 2022 to 2023, there were 489 finished consultant episodes (FCE) and 194 admissions for HD (ICD-10 code: G10), resulting in 8385 FCE bed days and 34 day cases.[18]

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended treatment options for HD. Currently approved treatments in the UK include: [19]

- Tetrabenazine for the symptomatic treatment of chorea associated with HD
- Olanzapine, a dopamine antagonist, for the treatment of motor and behavioral symptoms in HD

Similarily, guidelines have been developed in which a preference in prescription practice for using tiapride instead of tetrabenazine is noted. In severe chorea, combining two antidopaminergic drugs with a postsynaptic (e.g., tiapride) and presynaptic mode of action (e.g., tetrabenazine) has been highlighted as a potentially helpful strategy.[20]

Clinical Trial Information

Trial	**PROOF-HD; NCT04556656, EudraCT-2020-002822-10;** A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Arm, Multicentre Study Evaluating the Efficacy and Safety of Pridopidine in Patients with Early Stage of Huntington Disease **Phase III** – Active, Not Recruiting **Location(s)**: 8 EU countries, UK, USA, and Canada **Study completion date**: March 2024
Trial Design	Randomised, parallel assignment, quadruple-blind, placebo-controlled
Population	N=499; subjects with early-stage HD; adults aged 25 years and older
Intervention(s)	Pridopidine 45 mg oral capsules (twice daily)
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: - Change from baseline in the Unified Huntington Disease Rating Scale-Total functional capacity (UHDRS-TFC) score [Time Frame: Baseline, 65 weeks]
Results (efficacy)	PROOF-HD did not meet its primary endpoint, change from baseline compared to placebo at 65 weeks, as measured by the Unified Huntington Disease Rating Scale-

	TFC, or the key secondary endpoint, measured by the Composite Unified Huntington's Disease Rating Scale (cUHDRS) in all patients. Effects on both of these measures were reduced by the use of concomitant medications. Pre-specified analyses in PROOF-HD, excluding patients on neuroleptics and chorea medications, showed, clinically meaningful and nominally significant benefits or improvements from baseline of pridopidine as compared to placebo on disease progression, function, motor cognitive outcome measures. Q-Motor, an objective measure of motor function, showed robust beneficial effects for participants treated with pridopidine in PROOF-HD at various timepoints.[21]
Results (safety)	Pridopidine was well-tolerated with no serious treatment-related adverse events, with a safety and tolerability profile similar to placebo and consistent with previous clinical studies.[21]

Estimated Cost

The cost of pridopidine is not yet known.

Relevant Guidance

NICE Guidance

No guidance currently available.

NHS England (Policy/Commissioning) Guidance

No guidance currently available.

Other Guidance

- Guidelines of the German Neurological Society. Symptomatic treatment options for Huntington's disease. 2023.[20]
- European Huntington's disease network (EHDN). International Guidelines for the Treatment of Huntington's Disease. 2019.[22]
- European Huntington's disease network (EHDN). Clinical management of neuropsychiatric symptoms of Huntington Disease: Expert-based consensus guidelines on agitation, anxiety, apathy, psychosis, and sleep disorders. 2018.[23]

Additional Information

Prilenia did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development.

As a result, the NIHR Innovation Observatory has had to obtain data from other sources.

UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit.

We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.