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Newcastle University

Health Technology Briefing
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PXT3003 for treating Charcot-Marie-Tooth disease type 1A

Company/Developer	Pharnext SA

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 6814	NICE TSID: 9130	UKPS ID: 647201

Licensing and Market Availability Plans

Currently in phase II/III trials.

Summary

PXT3003 is currently in clinical development for treatment of patients aged 16-65 years with Charcot-Marie-Tooth disease type 1A (CMT1A). CMT is a group of inherited conditions that damage the peripheral nerves (reside outside the brain and spinal cord). CMT1 is characterised by muscle weakness and atrophy, which can lead to repeated ankle sprains, and changes in sensation which can cause clumsiness. CMT is a progressive disease meaning that the symptoms get worse over time. Currently, there is no specific treatment approved for CMT1A (symptomatic or disease modifying); current disease management options are limited to supportive care (such as leg braces, physiotherapy, anti-depressant, pain killer, surgery).

PXT3003 is a combination of three different ingredients that targets the specific mechanisms involved in the nerve abnormalities in CMT1A. It is formulated as an oral solution. PXT3003 could be effective in treating CMT1A as each ingredient interferes with peripheral myelin protein 22 (PMP22), which is overexpressed in CMT1A, expression differently. Together they downregulate the overexpression of PMP22, leading to improvement of neuronal signalling. If licensed, PXT3003 will offer an additional treatment option for patients with CMT1A.

Proposed Indication

Treatment for adult patients with Charcot-Marie-Tooth disease type 1A (CMT1A).[1]

Technology

Description

PXT3003 is a novel fixed-dose synergistic combination of baclofen, naltrexone and sorbitol. The three individual components of PXT3003 were selected to downregulate the overexpression of peripheral myelin protein 22 (PMP22) leading to improvement of neuronal signalling in dysfunctional peripheral nerves that are an essential part of the pathophysiology of CMT1A disease.[2]

PXT3003 is currently in pivotal phase III clinical development for patients aged 16-65 years with CMT1A in an international, multicentric, randomised, placebo controlled clinical study (the PREMIER trial). In the first phase III program (PLEO-CMT trial; NCT02579759 and PLEO-CMT-FU trial; NCT03023540) PXT3003 was being administered as liquid oral solution, 5 ml or 10ml twice a day.[1,3]

Key Innovation

Currently, there is no specific treatment approved for CMT1A (symptomatic or disease modifying) for CMT1A; current disease management options are limited to symptomatic treatment, such as medications for pain and fatigue, the use of support measures, such as ankle/foot orthoses and arm crutches, and corrective surgery.[4]

A combination of baclofen, naltrexone and D-sorbitol in low doses (PXT3003) could be effective in treating CMT1A as each agent interferes with PMP22 expression differently. Baclofen, a γ-aminobutyric acid (GABA)-B receptor agonist prescribed to relieve spasticity, acts via the cyclic adenosine monophosphate (cAMP)-dependent silencer element to negatively regulate PMP22 transcription in Schwann cells.[5] Low doses (0.1 mg/kg) of naltrexone, an opioid antagonist used to treat opiate and alcohol dependence, raise endogenous endorphin release, increase cell surface targeting of cognate opioid receptors, and are expected to potentiate the adenylate cyclase-inhibiting effect of endogenous opioids on the level of PMP22 expression.[6,7] D-sorbitol, a carbohydrate alcohol used as a sweetener in the food industry (E420) and as a laxative, can bind with high affinity to muscarinic receptors that are involved in PMP22 expression, and possibly improve protein folding.[8-11] Pre-clinical studies showed that PXT3003 limits PMP22 production, alleviates abnormal Schwann cell differentiation and improves neuromuscular function.[12] If licensed, PXT3003 will offer an additional treatment option for patients with CMT1A who currently have no effective therapies available.

Regulatory & Development Status

PXT-3003 does not currently have marketing authorisation in the EU/UK for any indication.

PXT-3003 is not in phase II/III clinical trial development for any other indication.[13]

PXT-3003 has been designated as an orphan drug in the EU since 2014 for the treatment of Charcot-Marie-Tooth disease type 1A.[14]

Patient Group

Disease Area and Clinical Need

CMT is a group of inherited conditions that damage the peripheral nerves. CMT1 is inherited in an autosomal dominant pattern. CMT1 is characterised by muscle weakness and atrophy, which can lead to repeated ankle sprains, falls and changes in sensation (paresthesia), which can cause clumsiness. Symptoms of this form of CMT usually start in childhood and mostly affect the periphery of the body, particularly in the feet, lower part of the legs, hands, and forearms. A subtype of CMT1 called CMT1A is caused by a duplication or, less commonly, a point mutation in the PMP22 gene on chromosome 17. Duplication of PMP22 gene leads to accumulation of the PMP22 protein, and point mutations alter its distribution. Patients with point mutations usually have more prominent clinical manifestations. PMP22 is vital for the normal creation and maintenance of the myelin sheath. CMT1 patients usually present with typical CMT onset within adolescence but remain ambulatory with no reduced life expectancy.[15] Symptom onset for individuals with CMT1A typically begins by the age of 20, and most often before the age of 10. However, there are still a lot of variabilities, with some people experiencing their first symptoms later in life, and others with identifiable symptoms at birth. Symptoms include a high arch and hammertoes, difficulty walking or running, symmetrical weakening and wasting of the muscles in the feet and lower legs (which can progress to the hands), numbness in regions of the body exhibiting muscle deterioration, and issues with balance.[16]

CMT is found worldwide in people of all races and ethnic groups. Prevalence rate estimates from epidemiological studies are highly variable due in part to the wide variation of clinical symptoms and different disease forms as well as discrepancies in what conditions are included within CMT. Recent prevalence estimates range from 9 to 28 per 100,000.[17] The prevalence of CMT1 is estimated to be between 1/7,000 and 1/5,000.[18] CMT1A accounts for around 70% to 80% of CMT1 cases, making it the most common subtype of CMT1.[15] In England (2021-22), for hereditary motor and sensory neuropathy (ICD-10 code: G60.0), which is also known as CMT, there were 275 finished consultant episodes (FCE), 224 admissions, which resulted in 1,142 FCE bed days and 98 day cases.[19,20]

Recommended Treatment Options

There is no specific treatment approved for CMT (symptomatic or disease modifying). There are some pharmacological therapies available to reduce symptoms of CMT, such as:[20]

- non-steroidal anti-inflammatory drugs, such as ibuprofen, for controlling pain
- tricyclic antidepressants or an anticonvulsant medication for neuropathic pain.

Clinical Trial Information

Trial	**PLEO-CMT, NCT02579759;** International, Multi-center, Randomized, Double-blind, Placebo-controlled Phase III Study Assessing in Parallel Groups the Efficacy and Safety of 2 Doses of PXT3003 in Patients With Charcot-Marie-Tooth Disease Type 1A Treated 15 Months **Phase III –** Completed **Location(s):** 5 EU countries, UK and USA **Study completion date:** August 2018	**PLEO-CMT-FU, NCT03023540;** International, Multi-center, Open Label, Follow-up Extension Study Assessing the Long-term Safety and Tolerability of PXT3003 in Patients With Charcot-Marie-Tooth Disease Type 1A **Phase III –** Active, not recruiting. **Location(s):** 4 EU countries, UK and USA **Primary study completion date:** December 2024
Trial Design	Randomised, parallel assignment, triple-blinded, placebo-controlled	Non-randomised, parallel-assignment, open-label

Population	N=323 (actual); patients with a proven genetic diagnosis of CMT1A; Mild-to-moderate severity assessed by Charcot-Marie-Tooth Neuropathy Score (version 2) with a score >2 and ≤18; aged 16-65 years old	N=187 (actual); patients previously randomized to study CLN-PXT3003-02 under placebo and dose 1 (LD) and having completed 15 months of double-blind treatment in that study, including all procedures required at the Study Termination visit (V6) or patients previously randomized to the initial study CLN-PXT3003-02 under dose 2 (HD), prematurely discontinued following sponsor decision, and having performed all procedures required at the Study Termination visit (V6)
Intervention(s)	Oral PXT3003 5 ml twice a day (bid)	Oral PXT3003 5 ml (Dose 1 / LD or Dose 2 HD) bid OR 10 ml (Dose 1 / LD) bid
Comparator(s)	Matched placebo	No comparator
Outcome(s)	**Primary outcome measure:** Overall Neuropathy Limitation Scale (ONLS) Total Score [Time frame: from baseline to month 15] See trial record for full list of other outcomes.	**Primary outcome measure:** Incidence of treatment-emergent adverse events (TEAEs) related to PXT3003 during the follow-up in patients with CMT1A [Time frame: 9 or 24 months]
Results (efficacy)	See trial record.	-
Results (safety)	See trial record.	-

Trial	**PREMIER, NCT04762758;** A Multi-center, Randomized, Double-blind, Placebo Controlled Phase III Study to Assess the Efficacy, Safety, and Tolerability of PXT3003 in Charcot-Marie-Tooth Type 1A (CMT1A) **Phase III –** Active, not recruiting **Location(s):** 6 EU countries, USA, Canada and Israel **Primary completion date:** October 2023
Trial Design	Randomised, parallel assignment, double-blinded
Population	N=350 (estimated); male and non-pregnant female subjects, with a genetically proven diagnosis of CMT1A who have mild-to-moderate severity assessed by a CMTNS-V2 score >2 and ≤18; aged 16 to 65 years
Intervention(s)	Oral PXT3003 10 ml bid (=PXT3003 HD of the PLEO-CMT Trial)
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** modified Overall Neuropathy Limitation Scale [Time frame: from baseline to Month 15] See trial record for full list of other outcomes

Results (efficacy)	-
Results (safety)	-

Estimated Cost

Cost of PXT3003 was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (adult). D04/S/a.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (adult). E06/S/a.

Other Guidance

No relevant guidance identified.

Additional Information

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