National Institute for Health Research

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PXT3003 for Charcot-Marie-Tooth disease type 1A

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LAY SUMMARY

Charcot-Marie-Tooth disease type 1A (CMT1A) is an inherited genetic disease in which the motor and/or sensory peripheral nerves are affected, resulting in muscle weakness and wasting, as well as sensory loss. These symptoms occur first in the legs and later in the hands. The nerve cells in individuals with this disorder are not able to send electrical signals properly because of abnormalities in the nerve or in the insulation around the nerve. Specific gene mutations are responsible for the abnormal function of the peripheral nerves. Over time, affected individuals may lose the normal use of their feet, hands, legs and arms. Common problems can include decreased sensitivity to heat, touch or pain, muscle weakness in the hand, foot or lower leg, trouble with fine motor skills, loss of muscle mass in the lower leg, and frequent tripping or falling. The disease is slowly progressive and variable, and those affected may have difficulties with every-day activities and may have a shorter life expectancy.

There is currently no cure for CMT1A, and treatments include physiotherapy, splints, occupational therapy and sometimes surgery. PXT3003 is a combination of 3 different ingredients that targets the specific mechanisms involved in the nerve abnormalities in CMT1A. It is formulated as an oral solution. If licensed, PXT3003 would be the first treatment for patients with CMT1A.

TARGET GROUP

Charcot-Marie-Tooth disease type 1A (CMT1A), mild to moderate - first-line treatment

TECHNOLOGY

DESCRIPTION

PXT3003 is a new low-dose fixed combination of baclofen, naltrexone and sorbitol. Its mechanism of action is multiple: a synergistic inhibition of the PMP22 gene overexpression associated with an improvement in myelination, preservation of the peripheral nerve axon and additional beneficial effects on other cell types: muscle cells, neuromuscular junctions and immune cells.[1]

PXT3003 is formulated using an approach called pleotherapy™ which systemizes the identification and development of new synergistic combinations of repositioned drugs for diseases with high unmet medical needs.

In the phase III clinical trial PLEO-CMT (NCT02579759)[2], PXT3003 is administered twice daily as an oral solution for 15 months. This is followed by further treatment for 9 months as established in the open-label extension study PLEO-CMT-FU (NCT03023540)[3].

PXT3003 does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

There is currently no curative or symptomatic drug for the treatment of CMT1A, and current management consists of supportive therapies including physiotherapy, orthotics, splints, occupational therapy and surgery.[5]

If licensed, PXT3003 will offer a treatment for adults (from 16 years old) with CMT1A.

DEVELOPER

Pharnext SA

AVAILABILITY, LAUNCH or MARKETING

PXT3003 was designated an orphan drug in USA in March 2014 for the treatment of CMT1A in adults.

PXT3003 was designated an orphan drug in EU in March 2014 for the treatment of CMT1A in adults.[4]

PATIENT GROUP

BACKGROUND

Charcot-Marie-Tooth (CMT) disease is a group of disorders in which the motor and/or sensory peripheral nerves are affected, resulting in muscle weakness and atrophy, as well as sensory loss. These manifestations occur first in the distal legs and later in the hands. The nerve cells in individuals with this disorder are not able to send electrical signals properly because of abnormalities in the nerve axon or abnormalities in the insulation (myelin) around the axon. Specific gene mutations are responsible for the abnormal function of the peripheral nerves. CMT disease can be inherited in an autosomal dominant, autosomal recessive or X-linked mode of inheritance.[5]

Symptoms of CMT disease usually begin gradually in adolescence, but can begin earlier or later. In almost all cases, the longest nerve fibres are affected first. Over time, affected individuals may lose the normal use of their feet, hands, legs and arms. Common red flags can include decreased sensitivity to heat, touch or pain, muscle weakness in the hand, foot or lower leg, trouble with fine motor skills, high-stepped gait (foot drop), loss of muscle mass in the lower leg, frequent tripping or falling, hammertoe, high foot arch and flat feet. Stretch reflexes may be lost. The disease is slowly progressive and variable and those affected may remain active for years.

Until now, it has been generally assumed that life expectancy of patients with CMT was unaffected by the disease. However, a recent Danish study of a large group of patients affected by CMT, and the first to use nationwide register-based data, revealed a significant increase in mortality. A 36% higher mortality rate was reported among patients diagnosed with CMT as compared with the general population.[6] In the most severe cases, breathing difficulties can hasten death.[5]

CMT1 is the dominant form of the condition in which nerve conduction velocities are slow. CMT1 is caused by abnormal genes involved in the structure and function of myelin. CMT1 has been further subdivided into CMT1A, CMT1B, CMT1C, CMT1D, and CMT1X, based on specific gene abnormalities. CMT1A is caused by a duplication of the PMP22 gene that is located on chromosome 17 at 17p11.2. CMT1A is the most common type of CMT1.[5]

CLINICAL NEED and BURDEN OF DISEASE

CMT prevalence in Europe is 0.03%, of which 57% have CMT1A; of patients with CMT1A, 78% are classified as having mild to moderate disease. Applied to the UK population, this equates to 7,100 patients who would be eligible for treatment with PXT3003.[a]

In addition, CMT can make everyday activities very difficult for patients and their families.[7] Patients suffer from progressive muscular atrophy of the legs and arms, resulting in walking, running and balance problems, as well as functional disorders of the hands. CMT1A patients can become dependent on a wheelchair in 5% of cases. They may also have mild to moderate sensory disturbances.[1] Living with a long-term, progressive condition can also have a significant emotional impact.[7]

[a] Information supplied by company.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

No guidance identified.

NHS ENGLAND and POLICY 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.

CURRENT TREATMENT OPTIONS

Treatments exist for many of the complications of CMT, but at present there are no disease-modifying therapies to either halt the progression or cure CMT. Current treatments include physiotherapy, orthotics, occupational therapy, pain and fatigue management and - when indicated - orthopaedic surgery, speech therapy and respiratory support.[8]

EFFICACY and SAFETY

Trial	PLEO-CMT, NCT02579759, CLN-PXT3003-02, EudraCT2015-002378-19; PXT3003 vs placebo; phase III	PLEO-CMT-FU, NCT03023540, CLN-PXT3003-03, EudraCT2015-002379-81; PXT3003; phase III extension
Sponsor	Pharnext SA	Pharnext SA
Status	Ongoing	Ongoing
Source of Information	Trial registry[2]	Trial registry[3]
Location	6 EU countries incl UK, USA and Canada	6 EU countries incl UK, USA and Canada
Design	Randomised, placebo-controlled	Patients randomised to PXT3003 dose 1 or 2 in the primary study will continue at the same dose (open label), while the patients who received placebo will be assigned to dose 1 at the entry in the extension study.
Participants	N=323; aged 16-65 yrs; Charcot-Marie-Tooth disease type 1A	All randomised patients who completed the primary study.

Schedule	Randomised to PXT3003 5ml liquid twice a day for 15 mths at 6mg baclofen; 0.70mg naltrexone; 210mg sorbitol daily, or placebo 5ml liquid twice a day for 15 mths.	Patients will receive PXT3003 dose 1 liquid twice a day for 9mths at 10ml.
Follow-up	Active treatment for 15 mths, then moved to extension study	Active treatment for 9 mths
Primary Outcomes	Disability measured by the change in the Overall Neuropathy Limitation Scale (ONLS) score (analysis of covariance on the summary mean of ONLS at 12 and 15 mths adjusted for baseline ONLS values	Incidence of treatment-emergent adverse events (TEAEs) related to PXT3003 during the follow-up [time frame 9 or 24 mths]
Secondary Outcomes	• Responder rate to PXT3003 therapy defined as a patient's improving on ONLS at end of treatment [time frame: 15 mths of treatment] • Arm and leg sub-items of ONLS [time frame: 12 and 15 mths] • Charcot-Marie-Tooth Neuropathy Score version 2 (CMTNS-v2) including its sub-items [time frame: 12 and 15 mths] • Nine-hole Peg Test performed on non-dominant hand [time frame: 12 and 15 mths] • Quantified Muscular Testing by hand grip and foot dorsiflexion dynamometry (mean of both sides) [time frame: 12 and 15 mths] • Time to walk 10m [time frame: 12 and 15 mths] • Compound Muscle Action Potential (CMAP) on ulnar or median nerves (non-dominant side) [time frame: 12 and 15 mths] • Sensory Nerve Action Potential (SNAP) on radial nerve (non-dominant side) [time frame: 12 and 15 mths] • Nerve conduction velocity (non-dominant side) [time frame: 12 and 15 mths] • Quality of Life - EuroQol 5-Dimensional Health-related	Time frame 9 or 24 mths: • Incidence of all TEAEs and their evaluation of type/nature, severity/intensity, seriousness, duration, relationship to study drug, and outcome • Incidence of adverse events leading to withdrawal of study drug • Overall Neuropathy Limitation Scale (ONLS) score, and its arm and leg sub-items • Charcot-Marie-Tooth Neuropathy Score - version 2 (CMTNS-v2) and its sub-items • Nine-hole Peg Test • Quantified Muscular Testing by hand grip and foot dorsiflexion dynamometry (mean of both sides) • Time to walk 10m • Compound Muscle Action Potential (CMAP) on ulnar nerve • Sensory Nerve Action Potential (SNAP) on radial nerve • Nerve conduction velocity • Quality of Life - EuroQol 5-Dimensional Health-related Quality of Life scale (EQ-5D)

	Quality of Life scale (EQ-5D) [time frame: 12 and 15 mths] • Visual analog scale on self-assessment of individualised main impairment in daily activities (defined at baseline with the patient) [time frame: 12 and 15 mths] • Safety and tolerability of PXT3003: assessment of some adverse event incidence and of the change in physical examination, vital signs, clinical laboratory variables, and ECGs [time frame: 15 mths] • Incidence of treatment-emergent adverse events (TEAEs), of related TEAE with moderate or severe intensity, AE leading to withdrawal of study drug, and Serious Adverse Events.	• Visual analog scale on self-assessment of individualised main impairment in daily activities (defined at baseline with the patient)
Key Results	Intermediate analysis by the Data Security Monitoring Board (DSMB) showed that the variability of tests between patients is within predefined limits. In addition, the futility analysis concludes that this trial is sufficiently powered to detect an effect of PXT3003 on the primary efficacy endpoint. The report also said that the intermediate analysis between blind variation analysis and futility analysis turned out a positive result.[9]	-
Adverse effects (AEs)	-	-
Expected reporting date	Estimated primary completion date reported as 4th quarter of 2018	Estimated completion date reported as 3rd quarter of 2019

Trial	NCT01401257, CLN-PXT3003-01; PXT3003 vs placebo; phase II
Sponsor	Pharnext SA
Status	Published
Source of Information	Abstract[10], trial registry[11]
Location	1 EU country, not UK

Design	Randomised, placebo-controlled
Participants	N=80; aged 18-65 yrs; Charcot-Marie-Tooth Disease type 1A
Schedule	Randomised to PXT3003 5ml liquid twice a day for 12mths in low dose (0.6mg baclofen; 0.07mg naltrexone; 21mg sorbitol daily), intermediate dose (1.2mg baclofen; 0.14mg naltrexone; 42mg sorbitol daily) or high dose (6mg baclofen; 0.70mg naltrexone; 210mg sorbitol daily); or placebo 5ml liquid twice a day for 12mths.
Follow-up	Active treatment for 12mths, follow-up 1 month
Primary Outcomes	Assess the clinical and laboratory safety and tolerability; number of participants with adverse events.
Secondary Outcomes	• To obtain preliminary data on the efficacy of PXT3003 on clinical scores and functional test, assessed CMTNS/CMTES: ONLS, VAS, fatigue, pain, six minute walk test (6MWT), nine-hole peg test, quantified muscular testing (QMT; hand grip and foot dorsiflexion), CGI [change from baseline after 3, 6, 9 and 12mths of treatment] • To assess the pharmacodynamic effect of PXT3003 on PMP22 mRNA levels and intra-epidermal axon density in cutaneous biopsy [change from baseline after 12mths of treatment] • To assess the pharmacodynamic effect of PXT3003 on selected neurophysiological parameters (sensory and motor responses of the median and ulnar nerves (non-dominant side)) [change from baseline after 3, 6, 9 and 12mths of treatment] • To assess the pharmacodynamic effect of PXT3003 on a series of biochemical markers in plasma [change from baseline after 3mths of treatment] • To assess the plasma concentrations of PXT3003 [after one administration and after 1, 6 and 12mths of treatment]
Key Results	This trial confirmed the safety and tolerability of PXT3003. The highest dose (HD) showed consistent evidence of improvement beyond stabilization. Charcot-Marie-Tooth Neuropathy Score (CMTNS) and Overall Neuropathy Limitation Scale (ONLS), with a significant improvement of respectively of 8% (0.4% - 16.2%) and 12.1% (2% - 23.2%) in the HD group versus the pool of all other groups, appear to be the most sensitive clinical endpoints to treatment despite their quasi-stability over one year under Placebo. Patients who did not deteriorate over one year were significantly more frequent in the HD group.[10]
Adverse effects (AEs)	None reported
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The anticipated price range is £10k-£15k per patient per year.[b]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs: *reduced use of secondary care/specialist services*

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

[b] Company confidential information.

REFERENCES

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