Press Release

Data from First Phase III Clinical Study of PXT3003 in Charcot-Marie-Tooth Disease Type 1A, the PLEO-CMT Trial, Published in the *Orphanet Journal of Rare Diseases*

PARIS, France, CET, October 18, 2021, 6:00 p.m. CET – Pharnext SA (FR0011191287 - ALPHA) (the 'Company'), an advanced late-stage clinical biopharmaceutical company pioneering new approaches to developing innovative drug combinations based on big genomics data and artificial intelligence using its PLEOTHERAPY™ platform, today announces the publication of the data from the Company's first phase III placebo-controlled clinical study of PXT3003 in Charcot-Marie-Tooth disease Type 1A ('CMT1A'), the PLEO-CMT trial, in the *Orphanet Journal of Rare Diseases* ('OJRD'). Based on their conclusion that the high-dose PXT3003 group demonstrated a statistically significant improvement in the primary endpoint, the Overall Neuropathy Limitations Scale ('ONLS'), compared to placebo, and a good safety profile, the authors state high-dose PXT3003 is considered a promising treatment option for patients with CMT1A.

The PLEO-CMT trial, an international, randomized, double-blind, placebo-controlled, Phase III study was designed to evaluate the efficacy and safety of high- or low-dose PXT3003 in patients with mild-to-moderate CMT1A, over a 15-month period. A total of 323 patients were enrolled in the PLEO-CMT trial in 29 centers across Europe, the U.S. and Canada. The high-dose PXT3003 group showed a significant improvement in the primary endpoint, the ONLS scale, *versus* placebo (mean difference: −0.37 points; 97.5% CI: [−0.68 to −0.06]; p=0.008), and consistent treatment effects were shown in the sensitivity analyses. Both the high- and low- doses were safe and well-tolerated. All randomized CMT1A patients who completed the PLEO-CMT trial (treated with PXT3003 or placebo) were eligible to pursue treatment with PXT3003 in an open-label follow-up extension study, the PLEO-CMT-FU trial. This extension study is still ongoing, and 130 patients are still receiving treatment with high-dose PXT3003.

Despite promising efficacy and safety data obtained in the PLEO-CMT trial, the U.S. FDA and the EMA have requested a second Phase III clinical study as a result of the premature discontinuation of the high-dose PXT3003 group due to an unexpected crystal formation in the high-dose formulation. The second international, randomized, double-blind, two-arm placebo-controlled Phase III study of PXT3003, the PREMIER trial, was initiated in March 2021 in the U.S. The dose of PXT3003 tested in the PREMIER trial *versus* Placebo equals to the high-dose tested in the PLEO-CMT and PLEO-CMT-FU trials. The main objectives of the PREMIER trial are to evaluate the safety and efficacy (on ONLS) of PXT3003 for the treatment of CMT1A. The trial will enroll approximately 350 subjects with mild-to-moderate CMT1A in 50 centers across the U.S., Canada, Europe, and Israel. As of today, almost 40 sites have been activated and are actively screening and enrolling patients with CMT1A. The trial is on track to complete enrollment in 2Q 2022 as initially planned. Topline results of this trial are expected to be announced in 3Q 2023.

The full title of the PLEO-CMT trial publication in the OJRD is: "*A double-blind, placebo-controlled, randomized trial of PXT3003 for the treatment of Charcot-Marie-Tooth type 1A*" (https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-02040-8).

Adrian Hepner, MD, PhD, Chief Medical Officer of Pharnext, said: "*We are pleased that the OJRD has published data from the PLEO-CMT trial and that the authors have concluded the high-dose PXT3003 group demonstrated a good safety profile and statistically significant improvement in the functioning of CMT1A patients, as evaluated by the ONLS,compared to placebo. This is further validation of our therapeutic candidate in CMT1A and we hope the efficacy and safety of PXT3003 observed in this first Phase III clinical study will be replicated in our ongoing pivotal Phase III PREMIER trial. We look forward to potentially making the first approved therapy for CMT1A available to patients in due course."*

Shahram Attarian, MD, PhD, Head of the Neuromuscular Diseases and ALS department at the University Hospital La Timone in Marseille (France), Coordinator of the FILNEMUS Rare Diseases Network and Neuromuscular Diseases Reference Centers in France, and Lead Investigator of the PREMIER trial in Europe, said: *"CMT1A is an indication with currently no existing approved therapies and I am delighted to be part of the clinical development program*

of this promising new therapy. The publication into the OJRD is very encouraging for the ongoing trial and I am grateful to all participants, their families and investigators for their support."

About Charcot-Marie-Tooth Disease Type 1A ('CMT1A')

Charcot-Marie-Tooth ('CMT') disease encompasses a heterogeneous group of inherited, severe, debilitating, progressive and chronic peripheral neuropathies. CMT1A, the most common type of CMT, is an orphan disease with a prevalence of 1/5000 people affecting about 150,000 people in Europe and the U.S. and about 1,500,000 people worldwide. The genetic mutation responsible for CMT1A is a duplication of the PMP22 gene coding for a peripheral myelin protein. The duplication of this gene results in overexpression of the PMP22 protein and failure of Schwann cells to produce normal myelin (neuronal sheath). The lack of a normal myelin structure and function leads to abnormal peripheral nerve conduction and axonal loss. As a result of peripheral nerve degradation, patients suffer from progressive muscle atrophy in both the legs and arms causing problems with walking, running and balance as well as abnormal hand functioning. They might also suffer from mild to moderate sensory disorders. First symptoms usually appear during adolescence and will progressively evolve throughout life. Patients with the most severe form of CMT1A end up in wheelchairs, representing at least 5% of cases. To date, no curative or symptomatic medications have been approved and treatment consists of supportive care such as orthotics, leg braces, physical and occupational therapy or surgery. More information can be found at https://pharnext.com/en/disease/charcot-marie-tooth.

About PXT3003

PXT3003 is a novel fixed-dose synergistic combination of baclofen, naltrexone and sorbitol formulated as an oral solution given twice a day. The three individual components of PXT3003 were selected to downregulate the overexpression of PMP22 protein, leading to improvement of neuronal signaling in dysfunctional peripheral nerves that are an essential part of the pathophysiology of this disease. PXT3003 could also have a positive effect on other cellular types of the motor unit such as the axon (direct protection), neuromuscular junctions or muscle cells. PXT3003 has shown promising and consistent results across preclinical and clinical studies in Phase II and Phase III (PLEO-CMT and PLEO-CMT-FU). More information can be found at https://pharnext.com/en/pipeline/pxt3003.

About the PLEO-CMT Trial

The PLEO-CMT trial was an international, randomized, double-blind, placebo-controlled, Phase III study evaluating the efficacy and safety of PXT3003 in patients with CMT1A, over a 15-month period. Two dose levels, named low dose ('LD') and high dose ('HD'), of PXT3003 in comparison to placebo were tested in patients diagnosed with mild-to-moderate CMT1A (HD equals double LD). A total of 323 patients were enrolled in 29 centers across Europe, the U.S. and Canada by December 2016 and last-patient-last-visit occurred in March 2018. Due to an unexpected issue in the HD formulation, the HD arm was prematurely stopped in September 2017. A revised statistical analysis plan was developed to take into account the premature HD arm discontinuation. Analysis of the primary endpoint, Overall Neuropathy Limitations Scale ('ONLS') from all investigated populations in the HD arm suggested preliminary efficacy in humans. The study further demonstrated the safety and tolerability of PXT3003. Further information on the PLEO-CMT trial can be found on the ClinicalTrials.gov website (study identification number: NCT03023540) here.

About the PLEO-CMT-FU Trial

All randomized CMT1A patients who completed the PLEO-CMT trial (treated with PXT3003 or placebo) were eligible to pursue treatment with PXT3003 in the PLEO-CMT-FU trial. This trial enrolled a total of 187 patients and was designed to primarily assess the long-term safety and tolerability of PXT3003. It was initially planned to be a double-blind, nine-month, Phase III follow-up extension study where patients treated with PXT3003 in the PLEO-CMT trial were eligible to continue their treatment at the same dose (High dose 'HD' or Low Dose 'LD'). Patients treated with placebo in the PLEO-CMT trial were randomized in PLEO-CMT-FU to receive LD or HD of PXT3003. Due to the PXT3003 HD formulation issue which occurred during the PLEO-CMT trial, the HD arm was discontinued in September 2017. Consequently, the PLEO-CMT-FU trial became an open-label study which is divided in 2 periods:

- Period 1 (9-month treatment period) from March 2017 to April 2019. Patients randomized to PXT3003 LD in PLEO-CMT continued on the same dose. Patients randomized to PXT3003 HD in PLEO-CMT continued on the same dose, but it was given as twice the volume of PXT3003 LD formulation after the PXT3003 HD formulation issue. Patients randomized to placebo in PLEO-CMT continued only on PXT3003 LD after the HD formulation issue.

- Period 2 from July 2018 (still on-going). The 153 patients who entered in PLEO-CMT-FU Period 2 were all switched to PXT3003 HD given as twice the volume of PXT3003 LD formulation.

In PLEO-CMT-FU, on top of safety and tolerability of PXT3003 which is evaluated every 3 months, long-term efficacy is evaluated with the ONLS measured every 6 months. Results from the PLEO-CMT-FU trial will be reported on a yearly basis.
Further information on the PLEO-CMT-FU trial can be found on the ClinicalTrials.gov website (study identification number: NCT03023540) here.

About the PREMIER Trial

The PREMIER trial is an international, randomized, double-blind, two-arm placebo-controlled, pivotal Phase III study, evaluating the efficacy and safety of PXT3003 versus placebo in mild-to-moderate CMT1A patients, over a 15-month period. The dose of PXT3003 tested in the PREMIER trial corresponds to the high dose ('HD') tested in the prior Phase III trial ('PLEO-CMT'). As agreed with regulatory agencies, the primary efficacy endpoint will be ONLS which measures functional motor disability. The secondary endpoints include the following outcome measures: 1) 10-Meter Walk Test ('10mWT'), 2) Quantified Muscular Testing (bilateral foot dorsiflexion dynamometry), 3) Patient Global Impression of Severity ('PGI-S'), 4) Patient Global Impression of Change ('PGI-C'), 5) Charcot-Marie-Tooth Neuropathy Score, version 2 ('CMTNS-v2'), and 6) Quantified Muscular Testing (hand grip). Safety and tolerability will be monitored throughout the study. Further information on the PREMIER trial can be found on the ClinicalTrials.gov website (study identification number: NCT04762758) here.

About Pharnext

Pharnext is an advanced clinical-stage biopharmaceutical company developing novel therapeutics for orphan and common neurodegenerative diseases that currently lack curative and/or disease-modifying treatments. Pharnext has two lead products in clinical development. PXT3003 completed an international Phase III trial with positive topline results for the treatment of Charcot-Marie-Tooth disease type 1A ('CMT1A') and benefits from orphan drug status in Europe and the United States. An international pivotal Phase III study of PXT3003 in CMT1A, the PREMIER trial, is currently ongoing. PXT864 has generated encouraging Phase II results in Alzheimer's disease and will be advanced through partnerships. Pharnext has developed a new drug discovery paradigm based on big genomics data and artificial intelligence: PLEOTHERAPY™. Pharnext identifies and develops synergic combinations of drugs called PLEODRUG™. More information can be found at www.pharnext.com.

Pharnext is listed on the Euronext Growth Stock Exchange in Paris (ISIN code: FR0011191287).

Disclaimer

This press release contains certain forward-looking statements concerning Pharnext and its business, including in respect of timing of and prospects for clinical trials and regulatory submissions of the Company's product candidates as well as a potential financing transaction, the use of proceeds therefrom and cash runway. Such forward-looking statements are based on assumptions that Pharnext considers to be reasonable. However, there can be no assurance that the estimates contained in such forward-looking statements will be verified, which estimates are subject to numerous risks including the risks set forth in Pharnext's URD approved by the AMF on November 9, 2020 under number N° R. 20-029 as well as in its annual periodic management reports and press releases (copies of which are available on www.pharnext.com) and to the development of economic conditions, financial markets and the markets in which Pharnext operates. The forward-looking statements contained in this press release are also subject to risks not yet known to Pharnext or not currently considered material by Pharnext. The occurrence of all or part of such risks could cause actual results, financial conditions, performance or achievements of Pharnext to be materially different from such forward-looking statements. Pharnext disclaims any intention or obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events, or otherwise.

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