PRESS RELEASE

END OF ENROLLEMENT OF THE 68 PATIENTS IN MEDESIS PHARMA PHASE 2 CLINICAL STUDY OF NANOLITHIUM FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Montpellier, October 17, 2023 at 8:00am CET – MEDESIS PHARMA, a pharmaceutical biotechnology company developing drug candidates based on its proprietary technology for administering active ingredients in nano micelles via the buccal route, Aonys®, announces the end of the 68 patient recruitment for its NanoLi AD study, evaluating the clinical safety and effectiveness of NanoLithium® NP03 in patients with mild to severe Alzheimer's disease, primary efficacy outcome should be known after 3 months of treatment in March 2024.

This proof-of-concept study evaluates the safety, tolerability, and efficacy of NanoLithium NP03 in patients with Alzheimer's disease in mild to severe stages. The main objective of this study is to assess clinical effect of NanoLithium compared to a placebo, on progression of behavioral and psychological symptoms associated with the disease between baseline and 12 weeks of treatment. This first efficacy outcome will be known in March 2024 after first interim analysis is conducted (once all patients complete 3 months of treatment). Secondary endpoints on cognitive symptoms and the pathological mechanisms of the disease (biomarkers and imaging) will be obtained at study end, in December 2024. The clinical trial is being conducted on 68 patients, with recruitment starting progressively in June 2022 in 8 French university hospitals (Toulouse, Montpellier, Marseille, Lille, Limoge, Lyon, Paris and Strasbourg).

Pr Maria Eugenia Soto Martin, Professor of Geriatrics and coordinator of the CMRR at Toulouse University Hospital, President of the French Federation of Memory Centres, Principal Investigator of the study and member of Medesis Pharma's Scientific Advisory Board, comments: *"The completion of enrolment in this Phase 2 trial represents a major milestone in the evaluation of a treatment strategy for Alzheimer's disease. The neuropsychiatric symptoms associated with the disease are a major complication of the disease, impacting the quality of life of patients and their caregivers, and one of the main reasons for avoidable hospitalization and institutionalization. These symptoms are very often present from the onset of the disease, and their early management has an impact on disease course. In this Phase 2 study, we are evaluating NanoLithium in Alzheimer's patients presenting early neuropsychiatric symptoms. This drug candidate holds promices by its dual potential acting both short term on these symptoms, but also longer term on more profound mechanisms of the disease, with a positive effect on cognitive symptoms. We are now looking forward to the follow-up period of the patients included, and to the main results of this trial. We are very grateful to the patients involved in the study and their families, to the investigators and to the clinical centers for their trust and participation in this important development program."*

Pr. Jacques Touchon, Professor Emeritus of the University of Montpellier, Co-editor-in-chief of the Journal of Prevention of Alzheimer's disease (JPAD), co-president and founding member of the Clinical Trials on Alzheimer's Disease (CTAD) conference; member of the scientific board of Medesis Pharma adds: *"Non-clinical studies have suggested that NanoLithium could be of interest in neurodegenerative diseases such as Alzheimer's, by acting not only on the mechanisms underlying psycho-behavioral symptoms, but also on the Alzheimer's disease pathlologenesis. In fact, it could act on several factors involved in the pathophysiological cascade responsible for neuronal degeneration (neuroinflammation, oxidative stress and, above all, anti-Tau action). The Phase 2 study, for which enrollement has been finalized, would support the potential of NanoLithium for the treatment of Alzheimer's disease, by acting not only on certain symptoms, but also on disease course."*

Dr. Jean-Claude Maurel, C.E.O and Founder of Medesis Pharma concludes: "*The end of patient recruitment in this clinical study for the treatment of Alzheimer's Disease is a crucial step for Medesis Pharma. Our NanoLithium product has demonstrated significant activity in several non-clinical studies, with very low doses of lithium, without signs of toxicity and suitable for prolonged treatment over several years. This study shall add clinical demonstration of the effectiveness of our microemulsion technology for buccal drug delivery. NanoLithium has a fine-tuning effect on multiple pathological factors involved in the disease and does not have hepatic metabolism, thus avoiding drug-drug interactions. It is a real innovation which could be part of the future landscape of Alzheimer's disease treatments alone or in combination. We thank the patients, their caregivers, the doctors and the teams from the 8 investigative centers who are continuing this important clinical study for patients and for our company".*

Studied drug: NanoLithium

This product is the formulation in the Aonys microemulsion of lithium citrate. Lithium citrate and lithium carbonate have been marketed for over 50 years for the treatment of Bipolar Disorder. The potential of lithium has been extensively studied and robust data support its use in the treatment of neurodegenerative disorders such as Alzheimer's disease. Lithium could have a beneficial effect not only on the psycho-behavioral symptoms associated with the disease, through its action on certain neurotransmitters but also on the evolution of the pathology itself, through a deeper regulation of pathological mechanisms (mainly inhibition of the pathway GSK-3β with an anti-Tau effect, reduction of neuroinflammation, regulation of oxidative stress, reduction of beta-amyloid protein, and overall neuroprotective effect)

Several scientific articles resulting from work carried out in collaboration with the Neuropharmacology Laboratory of McGill University in Montreal support the therapeutic activity of NanoLithium[1].

[1] Wilson EN, Do Carmo S, Iulita MF, Hall H, Ducatenzeiler A, Marks AR, Allard S, Jia DT, Windheim J, Cuello AC (2017) BACE1 inhibition by microdose lithium formulation NP03 rescues memory loss and early stage amyloid neuropathology. Transl Psychiatry 7, e1190.
Wilson EN, Do Carmo S, Iulita MF, Hall H, Austin GL, Jia DT, Malcolm JC, Foret MK, Marks AR, Butterfield DA, Cuello AC (2018) Microdose Lithium NP03 Diminishes Pre-Plaque Oxidative Damage and Neuroinflammation in a Rat Model of Alzheimer's-like Amyloidosis. Curr Alzheimer Res 15, 1220–1230. (.../...)
Wilson EN, Do Carmo S, Welikovitch LA, Hall H, Aguilar LF, Foret MK, Iulita MF, Jia DT, Marks AR, Allard S, Emmerson JT, Ducatenzeiler A, Cuello AC (2020) NP03, a Microdose Lithium Formulation, Blunts Early Amyloid Post-Plaque Neuropathology in McGill-R-Thy1-APP Alzheimer-Like Transgenic Rats. J Alzheimers Dis JAD 73, 723–739.
Guilliot, Solene et al. 'Lithium, a Treatment Option for Alzheimer's Disease? A Review of Existing Evidence and Discussion on Future Perspectives'. 1 Jan. 2023 : 1 – 10.

Advantages and perspectives of NanoLithium for the treatment of Alzheimer's Disease

The use of conventional lithium salts in older and fragile patients is very limited because of the narrow therapeutic window of these drugs (the toxic dose is very close to the effective dose). NanoLithium is really innovative, it optimizes the delivery of lithium into the cell, the doses used are 50 times lower than traditional doses. It holds potential to realize the therapeutic potential of lithium in this patient population, with the prospect of effective, non-invasive treatment with a positive safety profile.

Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder. It leads to progressive and permanent deterioration of nerve cells causing the most common form of dementia. This disease is common among older people, but it also affects young people. Alzheimer's disease is mainly known for one of the symptoms it causes: memory loss. But it is not limited to this simple cognitive deficit. Alzheimer's disease is, in fact, a progressive neurodegenerative desease with multiple symptoms (the nine signs of Alzheimer's disease are: language disorders; memory loss; loss of judgment; difficulty in planning or problem solving; withdrawal from work or social activities; disorientation; mood changes; difficulty accomplishing everyday tasks and inability to recognize familiar objects or people).

According to the World Health Organization, 55 million people suffer from dementia worldwide. Alzheimer's disease is responsible for 60 to 70% of cases. Dementia is the 7th leading cause of death on the planet. In France there are 1.2 million patients suffering from Alzheimer's disease.

The NanoLithium clinical study

This is a French proof of concept study, conducted in 8 clinical trial centers (Toulouse, Montpellier, Marseille, Lille, Limoges, Lyon, Paris and Strasbourg), prospective, multicenter, randomized (1:1), placebo-controlled, in groups parallel and double-blind. Patients will be randomized into two arms: NanoLithium NP03 (N=34); Placebo (N=34) over the first 12-week treatment phase. The study is then followed by a second 36-week period of open-label treatment for all patients in each arm.

The main objective (measured at 12 weeks) is to evaluate the effectiveness of NanoLithium NP03 compared to placebo, on the progression of neuropsychiatric symptoms measured using the Neuropsychiatric Inventory (NPI-12) score between inclusion and after 12 weeks of treatment.

The secondary objectives which will be evaluated throughout the study over a total of 48 weeks of treatment are to:

- Evaluate the safety of NanoLithium NP03 for 48 weeks (12 weeks for the double-blind period and 36 weeks for the open-label period) in patients with AD in mild to severe stages.
- Evaluate the effectiveness of NanoLithium NP03 on symptoms of agitation, progression of cognitive performance, progression of neuropsychiatric symptoms, progression of cortical hypometabolism in the parieto-temporal regions.
- Determine the potential effect of NanoLithium on progression of peripheric biomarkers of AD (amyloid-β protein, neurofilaments, pTau protein, Brain-Derived Neurotrophic Factor in plasma) and non-specific biomarkers (inflammatory cytokines).
- Evaluate therapeutic compliance.

Strategy for the development of NanoLithium

Further development (phase 3, registration and marketing) will be entrusted to a pharmaceutical partner. Contacts are underway with Pharmaceutical Laboratories and Biotechs in the United States, with a view to transferring a license option or a license through the agreement with the company Partner International.

About Medesis Pharma

To advance the treatment of serious diseases without effective treatments, Medesis Pharma creates drug candidates based on its proprietary Aonys® technology for the oral administration of active ingredients in nanodroplet form, enabling active ingredients to be effectively delivered to all cells, with passage through the blood–brain barrier (BBB).

This innovative approach is being applied to future drugs to treat major diseases that do not have effective treatments: Alzheimer's disease, Huntington's disease, and resistant cancers.

Medesis Pharma is also developing treatments dedicated to populations contaminated or irradiated after a civil or military nuclear accident.

French biopharmaceutical company based near Montpellier, Medesis Pharma is the author of 15 scientific publications, holds 12 patent families and 72 patents, resulting from 17 years of research.

Medesis Pharma shares are listed on Euronext Growth Paris: FR001844464 - ALMDP

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