PRESS RELEASE

Servier and Neurochlore announce the main results of the two phase 3 clinical studies assessing bumetanide in the treatment of Autism Spectrum Disorders in children and adolescents

Paris, 7 September 2021 – Servier and Neurochlore announce that no sign of effectiveness was observed in their two phase 3 clinical studies assessing bumetanide versus placebo in the treatment of Autism Spectrum Disorders (ASD) in children and adolescents. As a consequence, Servier and Neurochlore have decided, by mutual agreement, on an early termination of the two clinical studies in progress.

These two double-blind randomized phase 3 studies versus placebo were initiated 4 years ago in 14 countries, including 11 in Europe, within the framework of the Pediatric Investigation Plan (PIP) granted by the European Agency of Medicine (EMA). Thus, 422 children and adolescents with moderate-to-severe ASD, shared between the two studies, each with 211 participants according to their age (2-6 years and 7-17 years), were followed over 6 months in a double-blind placebo-controlled study, before being followed on bumetanide for an additional 6 months. It is the largest phase 3 European program dedicated to the treatment of core symptoms of autism in pediatrics.[1]

The results of these studies haven't demonstrated the superiority of bumetanide compared with placebo. None of the effectiveness criteria, both primary *(CARS - Childhood Autism Rating Scale)* and secondary *(SRS - Social Responsiveness Scale -, CGI Scale - Clinical Global Impression Scale -, Vineland)* were reached after 6 months of treatment, not in children aged 2-6 years or in children and adolescents aged 7-17 years. The studies didn't reveal any unexpected safety issue associated with the use of bumetanide.

These two phase 3 studies conducted by Servier followed a phase 2B trial sponsored by Neurochlore which was carried out in 6 centers in France in 90 autistic children and adolescents. The encouraging results from this clinical trial led to a partnership agreement between Servier and Neurochlore that was signed in March 2017, with the objective of developing bumetanide as the first treatment for ASD in children and adolescents.

"*We had high hopes for bumetanide, which had shown the potential to improve the core symptoms of children and adolescents with autism and the quality of life of their families. We are even more disappointed that today no pharmacological treatment exists to help these young children,"* explains

[1] The main criteria of assessment related to the core symptoms of Autism Spectrum Disorders and were alterations in communication and social interactions with the presence of stereotypical and repetitive behaviors.

Claude Bertrand, Executive Vice President R&D of Servier. *"We are pleased to have collaborated with Neurochlore on the development of bumetanide in the core symptoms of autism. This study program was carried out in an extremely rigorous manner, according to the highest standards of quality. We would like to thank the participating families, as well as the investigators and the centers for their involvement in the realization of these clinical studies."*

"The results of the phase 3 clinical studies are a major disappointment," declares **Professor Yehezkel Ben-Ari, President of Neurochlore**. *"Neurochlore's teams will now analyze in detail the results of the studies and potentially explore new approaches based on artificial intelligence, which may enable us to identify sub-populations of people suffering from Autism Spectrum Disorders, for whom bumetanide could be effective. The heterogeneity of ASDs probably makes it impossible to offer a sole treatment for all autistic children. We are proud of the work accomplished by the teams who conducted these studies. We would like to thank the children and their families who participated in the trials and for whom the medical need remains significant."*

About Servier

Servier is a global pharmaceutical group governed by a Foundation. With a strong international presence in 150 countries and a total revenue of 4.7 billion euros in 2020, Servier employs 22,500 people worldwide. Servier is an independent group that invests over 20% of its brand-name revenue in Research and Development every year. To accelerate therapeutic innovation for the benefit of patients, the Group is committed to open and collaborative innovation with academic partners, pharmaceutical groups, and biotech companies. It also integrates the patient's voice at the heart of its activities, from research to support beyond the pill.

A leader in cardiology, the ambition of the Servier Group is to become a renowned and innovative player in oncology. Its growth is based on a sustained commitment to cardiovascular and metabolic diseases, oncology, neuroscience and immuno-inflammatory diseases. To promote access to healthcare for all, the Servier Group also offers a range of quality generic drugs covering most pathologies. More information: servier.com

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About Neurochlore

Created 9 years ago by Dr Eric Lemonnier, Nouchine Hadjikhani, and Yehezkel Ben-Ari, Neurochlore is a biotechnology company dedicated to determining the molecular and cellular modifications in animal models with neurological and psychiatric diseases in relation with ionic exchanges. It is conveniently established within the Luminy scientific campus (biotech space). Doctor Honoris Causae of Liège University, Emeritus Director at l'INSERM (2009) and founder of L'INMED, Prof. Yehezkel Ben-Ari is world renowned for his work on ionic regulations in brain development and different pathologies, in particular ASD. Published in more than 500 scientific articles, his work has been honored by many awards, notably, the INSERM Grand Prize of Research (2009), and the Belgium FNRS (2012) and the grand prizes of American (2000) and European (2010) foundations of epilepsy. Neurochlore was able to carry out a single-center trial (2A) then a multi-center trial (2B) in 6 centers in France in more than 90 children with encouraging results in both trials. On an experimental level, Neurochlore employs around 20 people (researchers and technicians) and has invested all its grants in fundamental research well in advance of

potential applications, notably in the emergence of developmental brain diseases, that originate from a genetic or environmental pathogenic event occurring during pregnancy and/or birth. These are major public health issues that are very rarely studied at the molecular and cellular level.

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