

APM News - Neurochlore signs partnership with Servier for the development of bumetanide in autism

by Luu-Ly Do-Quang

PARIS, Mar 15 (APM) - Marseille-based biotech Neurochlore has signed a partnership with Servier for Phase III development and marketing of bumetanide in autistic spectrum disorder (ASD) in children, the biotech's founder professor Yehezkel Ben-Ari announced at a press conference.

The development programme follows on from positive results for a multi-centre Phase IIb study, published online in *Translational Psychiatry* on Tuesday (APMHE 52229).

"The terms of the agreement state that Servier will develop and market the product in Europe... The development plan includes three Phase III trials with an oral liquid form designed for children," the group said in a statement on Tuesday. "Servier will be in charge of the development plan currently under discussion with the European Medicines Agency (EMA). The aim is to obtain a marketing authorisation in 2021-2022," said Servier group vice-president in charge of business development and licensing Eric Falcand at Tuesday's press conference.

The development plan, for which Servier expects to have a response in April, involves the enrolment of 370 children aged two to 17 in several European countries, with one study of the younger children (aged two to seven) and another of those in the seven to 17 age group. Servier director of R&D for neuropsychiatric diseases Christian de Bodinat said the study should also document the way the effect is maintained over time.

Falcand said he would not provide the financial details of the agreement until EMA had given its response on the development plan. "It's quite a substantial plan, which will need tens of millions or even hundreds of millions of euros," he said. "What caught our interest is that for the first time we have hope of a treatment, whereas so far there has been no pharmacological treatment. Moreover, bumetanide is a known molecule, with a clearly identified mechanism of action," he continued.

Bumetanide is a loop diuretic that was approved in the 1980s and whose current indications include heart failure. Its benefits in autism were evaluated due to its effect on chloride, which is found at excessive levels in the neurones of autistic children at birth.

Ben-Ari said he was "highly satisfied" with the results shown in Phase IIb, as the chloride approach has "often been considered highly improbable". However, he stressed that bumetanide "is not a cure".

In the clinical study, and also according to the parents of the children in the first study who have now been monitored for seven years, bumetanide seems to "facilitate the children's participation in daily life and at school, and looking after them," said Dr Eric Lemonnier of the Limoges University hospital (CHU). "They are more 'present', contact is easier".

Regarding the safety profile of bumetanide, the main adverse event is hypokalaemia, which essentially occurs at the start of treatment. Asked by APM about biological monitoring of patients, Lemonnier said it is daily for the first week, then every two weeks for the following months and finally every six months.

"It is possible to compensate [for the hypokalaemia effect] by giving the children oral potassium, but for 70% of patients, equilibrium is achieved naturally. However, monitoring must be carried out throughout the treatment as in the long term there are potential effects on the liver, though so far, we have not had any cases," he added.

The Phase III studies are due to start in 2018 to confirm the efficacy of bumetanide in children with ASD. "We'll see about developing it for adult patients later on," Falcand said.

In the U.S., the Simons Foundation holds the rights to bumetanide. The U.S. Foundation invested in the Neurochlore project in 2012 and again in 2016.

Development in Parkinson's

The French biotech is continuing its R&D in autism and plans to develop a molecule targeting chloride without the diuretic effect of bumetanide, Ben-Ari said. He has founded a new biotech, B&A Therapeutics, to develop bumetanide in Parkinson's disease. The drug has been successfully tested in 74 patients by professor Philippe Damiere of the Nantes University hospital. The results were published in *Clinical Neuropharmacology* in early 2016.

The researchers aim to launch a Phase II clinical trial by the end of the year, Ben-Ari told APM. On the other hand, bumetanide failed to show efficacy in seizures in neonates with ischaemic encephalopathy (HIE) (NEMO study).

New research foundation

On the occasion of the presentation of the Phase IIb results for bumetanide in autism, Ben-Ari mentioned his project to set up a foundation to finance the research, as he has had difficulty finding partners.

The foundation has no name as yet but should lead to the setting up of a research centre in 2019 on the Luminy-Marseille campus, next to the Inmed Mediterranean neurobiology institute of which Ben-Ari is honorary director.

The aim is to stimulate translational research in the field of neurological and psychiatric diseases, especially the impact of the birth process on cognitive development, and to set up a think tank to develop new ideas and concepts.

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