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THE LHON AND WINDING ROAD

CHMP backs Santhera's Raxone in hereditary blindness condition

By Cormac Sheridan
Staff Writer

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DUBLIN – After a long and sometimes perilous review process, Santhera Pharmaceutical Holding AG has finally gotten Raxone (idebenone) across the line. At the second time of asking, the EMA's Committee for Human Medicinal Products (CHMP) voted in favor of its approval in Leber's hereditary optic neuropathy (LHON), paving the way for formal European Commission approval just over two months from now.

It's a significant milestone in the treatment of an ultra-rare condition for which no other therapy is currently approved. About 500 patients are newly diagnosed in Europe every year. Up to potentially 2,500 – those diagnosed within the past five years – could benefit from the therapy, Thomas Meier, CEO of Liestal, Switzerland-based Santhera, told *BioWorld Today*. "It's not a huge indication, but it is an attractive indication," he said.

The drug already receives reimbursement in France, where it obtained a temporary authorization in January 2014.

The rollout of the drug, which will commence shortly after formal approval is granted, will also help the company prepare for a hoped-for approval in Duchenne muscular dystrophy (DMD). In Europe, it will now be able to file for a variation – EMA-speak for a line extension – to the LHON marketing authorization. That has a shorter review time than a marketing authorization application.

"The path is much easier," Meier said. "If we are quick, and the CHMP works quickly with us, it could be at the back end of the first half of next year," he said. At the very least, a decision should come during the third quarter of next year.

More than 90 percent of LHON cases are caused by one of three mutations in the genes encoding complex I (NADH–ubiquinone–oxidoreductase) of the mitochondrial electron transport chain.

The result is inadequate ATP production, combined with the generation of free radicals that damage the energy-hungry retinal ganglion cells. That causes acute loss of central vision, first in one eye and shortly afterward in the second, and eventually leads to irreversible blindness.

"The mutations that cause LHON are rather mild if you compare them to other mitochondrial diseases," Thomas Klopstock, professor of neurology at the University of Munich, Germany, and the lead clinical investigator on the program, told *BioWorld Today*. "The penetrance of the mutations is rather low," he added. In males it is about 50 percent, whereas in females it is just 10 percent.

Raxone, a short-chain quinone, works by bypassing the defective complex I, enabling electron transfer to initiate at complex III. The goal of therapy is to stabilize, if not reverse, the disease process during the first five years after symptom onset, during which functional retinal ganglion cells persist.

Santhera originally filed for approval of the drug in another indication, the neuromuscular disorder Friedreich's ataxia, back in 2007, but the CHMP rejected the dossier. A subsequent phase III failure led to the withdrawal of the drug from the Canadian market, where it had received conditional approval.

Santhera sought approval in LHON in 2011, on the back of a randomized placebo-controlled study, Rhodos, in 85 patients. Although it failed to reach statistical significance in the intent-to-treat population, posthoc analysis showed that a subgroup of patients who at baseline had differing levels of visual impairment between their two eyes – a proxy for early stage patients – showed a significant improvement in visual recovery. That was not enough to convince the CHMP of its potential. (See *BioWorld Today*, Jan. 22, 2013.)

The filing of additional data from more than 90 patients included in an expanded access program, combined with natural history data from a survey of case records, helped its case a second time around. "These additional data were deemed valuable in the assessment of the application," Meier said.

The access program included patients who were within one year of symptom onset. "We saw recovery in 50 percent of patients," Klopstock said. "The spontaneous recovery rate was about 30 percent." The difference between the two was clinically relevant.

"The mean recovery is 19 letters," he said. "That's almost four lines." It can mean the difference between being able to use a computer or not. The drug will not be limited to patients in that category, however. "I don't want to exclude [the possibility] that patients could not benefit in the second or third year," Klopstock said.

EXCEPTIONAL CIRCUMSTANCES

The CHMP is recommending approval under the EMA's Exceptional Circumstances measure, which it also invoked when granting approval to Amsterdam, the Netherlands-based Uniqure NV's gene therapy treatment for familial homozygous hypercholesterolemia Glybera (alipogene tiparvovec).

"The Exceptional Circumstances [rule] is used in cases where comprehensive datasets cannot be collected in a reasonable period of time," Meier said. Santhera will conduct a post-approval, open-label trial and will open a patient registry to enable it to build natural histories of those on the drug. But the small patient population will limit its scale.

The news caps a turnaround in Santhera's fortunes that has been under way since the company reported positive phase III data in DMD. (See *BioWorld Today*, May 14, 2014.)

Shares in Santhera (ZURICH:SANN) edged back about 3 percent on the news, as some investors banked their profits. The stock is up by more than 150 percent in the last year – it is currently valued at CHF457 million (US$490 million) and was valued at just CHF7.9 million back in January 2013.

The company has just CHF14 million on its balance sheet. Although it has not yet announced any plans to raise more cash, doing so "would be a logical step," Meier said.

And the job of the newly appointed chief financial officer, Christoph Rentsch, has just gotten easier.