Evaluate Vantage

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EP Vantage interview – Repurposing gives NeuroVive entrée to mitochondrial medicine

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Mitochondrial medicine is on the cutting edge of biotech research, and yet NeuroVive Pharmaceutical finds itself in late stage trials with a potentially mitochondria-protecting product by repurposing an old compound, the immunosuppressant cyclosporine.

The Swedish group hopes its lead drug, the reforumulated cyclosporine called CicloMulsion, will prove effective for cardiac reperfusion injuries in its 1,000-patient European phase III trial. If successful, it could be the first pharmaceutical treatment to prevent heart tissue damage resulting from the return of blood flow: “We are at the frontier,” says NeuroVive chief executive Mikael Brönnegård. “There are a number of phase II trials with other products. But they have to go into phase III.”

Happy accidents

Much of what brought NeuroVive to the cusp of having a clinically-proven cardiovascular drug has been accidental, starting with cyclosporine’s isolation by Sandoz scientists from a fungus found in a Norwegian soil sample in 1969. It was first used as an immunosuppressive in transplant patients under the name Sandimmune by Sandoz and then Novartis.

Two decades later it was found to be a neuroprotectant by Eskil Elmér, NeuroVive’s founder and chief science officer, who was running central nervous system cell-survival tests. That discovery led to development of the company’s second product, NeuroStat, targeting secondary traumatic brain damage following head injury.

The compound prevents cell damage and death from ischaemia injury by binding with cyclophilin D, which modulates mitochondrial permeability. During ischaemic injury, the mitochondria become more permeable, allowing calcium to flow in and destroy the mitochondria.

CicloMulsion has come to NeuroVive from the work of surgeon Michel Ovize at the University of Lyon, in its own roundabout way. Dr Ovize had completed phase II trials in reperfusion injuries using Sandimmune, but Novartis had declined to provide product and a placebo for a phase III trial. Dr Ovize contacted NeuroVive because it had formulated cyclosporine without use of the stabiliser Cremaphor, which carries a risk of anaphylaxis.

NeuroStat and CicloMulsion are essentially the same formulation, the difference being in bottle size for dosing: CicloMulsion is a single dose product at 2.5mg/kg, whilst NeuroStat will be a bolus dose plus five days of further treatment.

Thus the company finds itself in the fortunate position of having a clinical candidate in advanced stages of development with its R&D expenses limited to the cost of providing the product, a position most biotechs would envy.

“This is of course a bonus for us,” Mr Brönnegård says.

Fundraising

If NeuroVive has been fortunate in having the CicloMulsion trial largely paid for, it is in keeping with a rather economical approach to clinical development. Last year the company reported that it spent SEK15.1m ($2.28m) and the year before SEK7.88m; Mr Brönnegård estimates current cash holdings at about €5m ($6.6m). It has been able to do so by keeping staffing levels low – four full time employees - and relying on outside consultants, he says.

“I’m very surprised that people make this mistake,” he says. “They found a company. They have an excellent idea and then they get some money to finance the operations. Then they start to hire people. And immediately the burn rate goes up.

“I used to work as a venture capitalist. That was not a good signal at all for me as an investor if you had an

early stage company."

NeuroVive does, however, have its eyes on becoming something other than an early-stage company. It is currently listed on the AktieTorget trading platform, but in April will move to the Nasdaq-OMX market, allowing it to access institutional investors. That will set the stage for a planned fundraising in the second half of next year in which Mr Brönnegård hopes to raise somewhere in the range of $40m-$50m.

That financing, should it come through, would be used to finance clinical development of its remaining pipeline to phase IIb or phase III. The remaining pipeline has a mitochondrial medicine focus, with Mr Brönnegård pointing to a developing collaboration with the Philadelphia Children's Hospital for the rare mitochondrial disease complex 1 deficiency.

Developing the business

More immediately, the concern is going to market with CicloMulsion should Dr Ovize's trial succeed. NeuroVive has already signed a collaboration with Sihuan Pharmaceutical to develop and market both of its cyclosporine-based products in China.

In Europe, a collaboration with the clinical research organisation Quintiles has yielded a go-to-market plan, Mr Brönnegård says. As a product to be used in hospitals the necessary sales force would be small by comparison to one that would need to be marketed to office-based physicians, and well within the capability of a collaboration between the two if the CRO were to extend the existing arrangement.

Mr Brönnegård says less about the US, although a big pharma marketing partner would probably be more necessary in the world's biggest drug market. Strong results from Dr Ovize's trial would make that job easier, of course; a presentation of phase II data at the AHA scientific sessions has no doubt primed the pump.

Given the modest investment, a failure for CicloMulsion would probably not be a huge disappointment for NeuroVive, although it could cast some doubt on the potential of NeuroStat to prove effective in preventing brain damage. But having gotten so far by repurposing an old drug, NeuroVive prefers not to step backward and become an early-stage company all over again; its next generation of mitochondrial medicine may not come so cheap.

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