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Resetting After Your Lead Drug Fails

By Lucie Ellis

Santhera CEO On Transparency In The Face Of Adversity

BECOMING A FIRST-TIME CEO OF A biotech company in 2020 meant dealing with unexpected challenges without any instruction book to follow. Santhera Pharmaceuticals' Dario Eklund not only had COVID-19 upheaval to manage, but also a late-stage trial failure, a virtual financing and a new plan for the company to sell to stakeholders.

When Dario Eklund joined Santhera Pharmaceuticals as CEO in December 2019, he could not have prepared for what his first year would bring. Amid a pandemic, he has had to deal with an unexpected Phase III failure of the firm's lead product, while trying to make his mark upon the firm. "Ihave learned a lot in this past year, perhaps more than from several years in other roles."

Eklund has worked in biopharma for more than 25 years, for big and small businesses, private and public, in both the US and Europe. He was attracted to Santhera because of the company's focus on rare diseases, with a pipeline directed toward Duchenne muscular dystrophy (DMD) and cystic fibrosis.

Prior to this, he was chief commercial officer of Vifor Pharma Group with full P&L responsibility for a global business with turnover in excess of CHF1bn ($1.1bn) and more than 1,000 employees. A full year into his first CEO position, he discussed with In Vivo the trials and triumphs of 2020.

The Bearer Of Bad News

In November 2020, Santhera formally withdrew its European marketing authorization application (MAA) for idebenone following its decision to end development of the drug as a potential treatment for DMD. The company decided to halt the program earlier in 2020 after a futile interim analysis indicated that idebenone would be unlikely to meet the primary endpoint of the Phase III SIDEROS study. DMD is one of the most common and severe forms of muscular dystrophy. It usually affects boys and is diagnosed in early childhood; people with the condition will usually only live into their 20s or 30s. (Also see "Santhera Pulls EU Filing For Failed DMD Candidate" - Pink Sheet, 11 Nov, 2020.)

Idebenone was known as Puldysa in the DMD setting. It is already approved as Raxone for the treatment of Leber's hereditary optic neuropathy (LHON). In May 2019, Santhera licensed Raxone to Italy's Chiesi Farmaceutici S.p.A. for LHON to enable it to concentrate on the DMD development program.

The failure of the late-stage SIDEROS trial was an unexpected challenge for Eklund in 2020. There were three outcomes from the interim analysis that Santhera had considered. The first outcome could have been very high statistical significance. In that case, the company

would have aborted the study early because the drug was so effective. "We were always hoping for that scenario," Eklund noted. The second scenario could have been a clear difference between the treatment and placebo groups, but not with enough evidence to end the study earlier than planned. Then the third option could be no difference between the placebo and treatment groups – futility.

"We were quite certain one of the first two scenarios was going to kick in based on the previous and successful DELOS study analysis at the equivalent time point," Eklund recalled. "We were very bullish that either of the two successful outcomes was going to be the reality. And in the end, we were faced with this futility. We weren't prepared really for that scenario."

When the interim analysis from the registrational Phase III study failed to show positive results for what was its lead pipeline candidate – and, moreover, a drug for which it was already scaling up commercial operations – the company needed to act quickly. "We spent the whole night putting together communications to all the various stakeholders," Eklund said. The company needed to prepare information for the board, investors, patients, parents and caregivers, investigators, patient advocacy groups and its staff. "The employees of the company were devastated because they had been working hard for many years to develop the drug, and now suddenly … it was not going to be successful in terms of bringing in new therapy to market."

Late into the night, Eklund also needed to convince Santhera's board to approve his restructuring plan. "We were originally planning to launch the drug in the first quarter of 2021. So, we had marketing and commercial teams already in place in nine countries. We were ready to go." After discontinuing development of Puldysa, Santhera laid off around half of its workforce.

Meetings with staff and stakeholders continued for several weeks. "I think it's extremely important that when you are in a crisis situation like this, that you are communicating as transparently as you possibly can; that you're not trying to put a spin on it," Eklund said. He focused on managing expectations and getting a plan in place to take the company forward. "You're trying to create as much clarity into a very dusty situation as you possibly can."

Eklund also highlighted the issue of relaying bad news to patients. "We've had a deeper discussion with patient advocacy groups who told us, 'Look, our patients found out about this interim analysis showing futility by reading a press release, and they should have heard it from their doctor.' I totally sympathize and empathize with them on that. But the problem is that we're a publicly traded company."

The situation was very fast paced: Santhera found out on a Monday evening from the data safety monitoring board about the poor SIDEROS data readout and had to disclose this information before the next morning. "There's not a lot of opportunity for a publicly traded company to go and inform the doctors and the patients about the findings before it becomes public knowledge" because of financial regulations.

Debutant CEO In The Time Of COVID

When Eklund joined the company there was no chief financial officer in place; this role was filled in Q2 of 2020

when Andrew Smith joined the business. "In that first period of my role here, I was without a CFO and in a situation where we didn't have enough money to take us to the next inflection point." Santhera only had enough cash to take it to around April 2020, a few months shy of the time it had originally hoped to receive a positive European regulatory opinion from the CHMP for Puldysa.

"Going through that exercise without a CFO … was a tremendous learning. In a publicly held company, there's a lot more pressure and there's a lot more exposure." Eklund held over 100 meetings with potential investors during his first few months at the company, before COVID-19 halted travel.

Raising traditional equity investment was difficult as Santhera has a CHF60m convertible bond debt that was issued in 2017 and is due in 2022 which can scare off equity investors who do not want their money to be spent on paying back debt rather than growing a business. "We need to restructure that debt with bondholders in Q1 2021 ahead of the next equity raise."

Still, Santhera raised cash throughout 2020 from various sources, but also managed to secure CHF20m in June from Highbridge Capital Management through the issuance of senior secured exchangeable notes; it now has a cash runway out to around Q2 2021.

During the start of the COVID-19 pandemic, raising money from his "bedroom" was not easy, Eklund noted. "You need to coordinate a lot of due diligence calls, need to coordinate a lot of lawyers on both sides, and so on. There's a greater degree of difficulty in fundraising when you're in a COVID environment."

However, Eklund thinks some of the changes seen in 2020 around biopharma funding will remain in the future, even as the world moves back to pre-COVID activities. "It's going to be easier in the future to raise money because we won't have to do roadshows like we used to do in the past, where you'd fly over to the US and spend a week physically sitting in a taxi from meeting to meeting in New York and then do the same in Boston, and then fly to do the same thing in London. It's a lot more efficient now where you can do these corporate presentations and discussions online."

Eklund added that Santhera expected to continue internal operations with some form of remote working. "I was absolutely clear that we will be working more from home. Even when we are not in lockdown anymore. The office is the hub, you can come here if you need to have a meeting, if you want to have quiet, if you want to have a different space where you can work then you can come to the office, but it's not by any means mandatory."

People Management

Taking over as CEO, Eklund hoped to put his own stamp on Santhera – another thing made more difficult by COVID-19.

"When you're a new CEO, you want to introduce the culture that you want to establish in the company. And that culture comes from you, from symbolic gestures, how you behave in meetings, how you treat people, how you're visible or not visible in the company," Eklund said. "And you learn a lot about people by walking around; you drink coffees, you chat, and you can see the subtle body language in meetings. All of this educates you about the people that you're working with and the culture at the company."

In the COVID-19 era, however, "You're not able to walk into somebody's office casually and just have a cup of coffee. In Zoom meetings, it's sometimes difficult to read subtle cues, body language cues, it's very difficult for a leader to assess how overworked people are or not, for example. And so that whole leadership aspect is more difficult in a COVID environment."

As a leader it was critical to provide constructive and reinforcing feedback to employees, Eklund continued, but this is challenging when most staff are working remotely.

"You need to provide feedback to your team in a balanced way so that they don't reject it, that they listen, because of constructive discussion. When you're doing it in a COVID environment, in a remote setting, you don't see them as much. It becomes very difficult for a leader then to provide that oversight and provide that balanced feedback when you're operating in a world where you have much less exposure to people on a daily basis."

Being Prepared And Moving On

Looking back on his journey and that of Santhera in 2020, Eklund said his key takeaway was to always be prepared. "It is kind of obvious, but it is really important to be prepared for every scenario." He said one key lesson was to have more discussion in advance on the messaging for each scenario, especially with bad news as a possibility. "There can't be cognitive dissonance or misinformation, because that creates a lot of uncertainty." Despite futility being the unexpected and unprepared for outcome of SIDEROS, Eklund thinks the company did a good job handling the bad news. "You can always improve, and this is certainly a learning that I will take with me to any future role."

Having discontinued development of Puldysa, Santhera needed a new focus. In September 2020, the company exercised an option it held to obtain worldwide rights to a new drug for DMD, vamorolone. Santhera obtained an exclusive license from its originator ReveraGen for all indications worldwide. It believes vamorolone is the only "dissociative" steroid in clinical development, defined because of the dissociation between transrepression and transactivation. The aim is to provide similar (or increased) efficacy but with fewer side effects.

A pivotal Phase IIb study is ongoing for the drug in DMD patients, with a six-month data readout expected in the second quarter of 2021. If successful, the results could lead to an NDA submission with the FDA in the fourth quarter of 2021, which is subject to a fast-track review. Santhera anticipates being the first to market with a dissociative steroid in the US in 2022.

Santhera, is developing vamorolone for early stage DMD patients requiring an anti-inflammatory, muscle strengthening treatment with a favorable tolerability profile to make it suitable for longer term administration and improved compliance. Vamorolone binds to the same receptor as corticosteroids but modifies its downstream activity. The company said vamorolone "could emerge as a foundational therapy in DMD for all patients irrespective of gene mutation and a promising alternative to existing corticosteroids, the current standard of care in children and adolescent patients with DMD."

If the drug is successful in treating DMD patients, Eklund noted its potential for other indications where patients are regularly using steroid treatment, such as COPD, asthma, ulcerative colitis and Crohn's disease. He said vamorolone "is actually more attractive" than Puldysa. He noted that the existing market for corticosteroids was a benefit, with a commercial path already laid out in DMD and other indications. "Today, we have new management, we have a new CFO … we have a new asset which has higher peak sales estimates, a more straightforward clinical and regulatory pathway, a market that already exists, and a lower-risk commercial strategy."

Looking into 2021, Eklund said the company would focus on development of vamorolone and potential partnering opportunities, such as commercial arrangements for marketing the drug in other geographies like China and Japan. Also, development deals for vamorolone in other indications beyond DMD.

The company will also need to raise more cash to take vamorolone through to regulatory filings, potentially with a dual listing on NASDAQ on the cards for 2022. The company will also need to strengthen its US presence as it shifts gears. "We had our commercial team on the ground in Europe … Now we have become a more and more US-centric company, but we are still headquartered in Switzerland. Our commercial efforts and the weight of the company will be much more geared towards a US launch."