Charles Stacey – President & CEO, Cerecin

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17.05.2021

Tags: Singapore, Cerecin, CNS, Alzheimer's, Biotech, Strategy

Cerecin's Charles Stacey outlines the company's progress in expanding its lead asset into migraine and infantile spasms, how its funding strategy has evolved, why Singapore is still a logical base, and how broader developments in the CNS landscape stand to benefit all stakeholders.

Charles, the last time we spoke in 2018, Cerecin had recently rebranded, relocated to Singapore from the USA, and got a new investor on board. What has happened since then, and where does Cerecin stand today?

Cerecin was founded in 2000 and moved its company headquarters from the USA to Singapore in 2018. Three things drove that move:

1. We were doing an increasing number of clinical studies, a sizeable proportion of which were in Asia; therefore, it made sense for us to have a clinical base here.
2. Establishing our manufacturing and supply chain in this part of the world, especially given that one of our key raw materials comes from Southeast Asia.
3. Recognizing that there is a growing hub of biotech activity within Singapore, with good access to capital and talented individuals.

Three years down the line, these fundamentals still hold firm. Things have played out as well as we could have hoped for in the Lion City.

The majority of our executive and operational team now sit in Singapore, spread across our core functions of R&D and clinical operations. Additionally, all the back-office staff supporting our executive team are here, and the US. Establishing this team in Singapore has been key to our core activities, the launch of Asia focused programmes.

Back in 2018, we spoke predominately about our work in Alzheimer's, which has progressed well. We have conducted several studies in preparation for a global Phase III study that was due to start in 2020, but like many other clinical trials, needed to be placed on hold due to the COVID-19 pandemic.

When back up and running, this will be a huge study, involving over 100 sites globally, but with a very vulnerable patient population. Given the complexity and logistics involved, postponing the study and protecting elderly patients from risks associated with the virus, was the right thing to do.

In parallel, we have started studies in other indications, with two programs, one in migraine prevention which is up and running, and a second program in infantile spasms, an orphan form of paediatric epilepsy.

We saw that the USA FDA recently granted Cerecin's lead asset Rare Paediatric Disease and Orphan Drug designations for infantile spasms. Can you talk us through the progress made in therapeutic areas other than Alzheimer's disease?

Our lead compound *tricaprilin* is a ketogenic drug, a structured lipid, that provides an exogenous source of ketones. These ketones provide the brain with an additional source of energy as well as act as important signalling molecules.

For the first ten years or so of the company's life, the focus of our drug development was on Alzheimer's disease. However, we always recognized the potential therapeutic benefits of ketones were far broader than just Alzheimer's, but, as a smaller company, we had to have a narrower initial focus to develop proof of concept and move programs along.

One of the core components of our plan has been to expand *tricaprilin* to other indications. There are many reasons for this; Alzheimer's disease is a large indication and one of the big blockbuster indications left to crack, but it is challenging. Therefore, we want to include other indications within our pipeline and portfolio that expand the market potential and provide diversification.

In 2019, we performed a comprehensive review of all the neurological indications in which there is evidence that our ketogenic mechanism – through the use of ketogenic agents or the ketogenic diet, could have efficacy in treating the disease. We also considered several other factors including how the indications sat together within our pipeline.

Through this process, we narrowed the indications down to migraine prevention and infantile spasms.

Migraine, like Alzheimer's disease, is another large indication affecting millions of patients worldwide. Unlike Alzheimer's disease however, migraine has seen the recent approval of a new class of drugs, CGRP receptor antagonists, that are having a significant impact on how this disease is managed.

With two large indications decided on, our next aim was an orphan indication, potentially with expedited regulatory approval. The most well recognised group of orphan indications where the role of the ketogenic diet is well-established are several rare seizure disorders. Therefore, we sought an orphan indication within epilepsy. The ketogenic diet is often used as a second- or third-line treatment. Hence, we began animal work back in 2018-19, establishing efficacy within some preclinical studies and, based on that, filed Orphan Drug Designation and Rare Pediatric Disease designation for the use of tricaprilin in Infantile Spasms, with the FDA.

How well-established is the ketogenic diet as a treatment option for neurological disease, beyond it being a fashionable weight-loss regime?

Five to ten years ago, we would spend the first half-hour of any meeting explaining what the ketogenic diet was. The situation has changed, and today, when we mention ketones, the response is often "Oh, I'm on the ketogenic diet!"

The diet causes a person to develop endogenous ketosis, raising ketone levels, leading to weight loss. People on the diet also experience other beneficial effects on the brain.

The diet was originally developed at the Mayo Clinic in the 1920s to treat drug-resistant epilepsy, and researchers found the diet to be effective in a subgroup of patients who were unresponsive to medication. The diet is incredibly restrictive – 70-80 per cent of intake is fat, and 10-20 is carbohydrates – which leads to an increase in ketones. There is a huge body of evidence to support its effectiveness in epilepsy, and most of the leading epilepsy centres today have departments specializing in the nutritional establishment and maintenance of the ketogenic diet.

Keto in Alzheimer's disease is slowly becoming more recognised. A 2020 review paper looked at the role of this diet within Alzheimer's, reviewing 11 animal studies and 11 human studies. The current literature shows some degree of efficacy and improved cognitive symptoms if patients persist with the diet. They will show an increase in plasma ketone levels, which often correlates with cognitive benefit.

The challenge in shifting Alzheimer's patients to a ketogenic diet is compliance. Unlike children, who will eat what they are given, Alzheimer's patients tend to be elderly, already confused, and have a preference for sweet foods. Here, an obvious role for Cerecin's agent is established because patients do not need to have any form of dietary restriction, can leverage the same mechanism, and potentially achieve the same result, despite maintaining a normal diet.

Last time we spoke, you also mentioned that you had an established medical food product in certain markets. Is this still ongoing, and is the idea of covering the full spectrum of Alzheimer's care still an area of focus?

When I joined in 2015, the company was more commercially focused on medical foods. My main objective has been to transition Cerecin into a traditional pharmaceutical company, focused exclusively on the drug product *tricaprilin*.

Our commercial strategy for the medical food product is centred in Asia and is conducted entirely through partners. In the right markets, medical food products can be very successful, but it depends on many factors include; culture, healthcare practices and regulation. We rely on our highly experienced partners to understand the market and decide how to position the product, while we focus exclusively on drug development.

This drug development focus is made possible by Cerecin's strong R&D team. In our industry, the only way to establish clinical credibility and validity is the standard path to pharmaceutical regulatory approval. This gives physicians the confidence to prescribe a drug, patients the confidence to take it, and payers the confidence to pay for it and ultimately. get it into the hands of millions of people.

In our recent conversation with Jean-Paul Clozel of Idorsia, he talked about how focusing on small molecule drug development in a world seemingly driven by large molecules makes sense as these technologies are more established, less expensive and

have a better chance of making it to market. Does this ring true for Cerecin as well and what differentiates your strategy?

Absolutely. Alzheimer's disease is a challenging space with a number of drug development failures – particularly in later stages – over the past decade. This is because there has been too much focus on one target and mechanism – amyloid. A successful drug development in any indication needs mechanism diversity, in whch multiple targets are being tackled.

At Cerecin, our approach is differentiated from most other programmes and we believe it is significantly de-risked. When you develop a drug product, you must think about two things. The first is safety – particularly in Alzheimer's patients, who are elderly, with comorbidities, and who may need multiple medications – and the fact that this is an ongoing disease where patients will need to take a drug for a long time. Our API is a structured lipid, so we are leveraging a physiological pathway that occurs naturally in our bodies. When we go to sleep at night and do not eat for eight to ten hours, our bodies produce ketones. We utilize the same pathway, not introducing potentially toxic chemicals that act on atypical pathways.

The other key concern is efficacy. Our analogous studies with the ketogenic diet and our comprehensive Phase II program mean that the process is de-risked. Moreover, support around the ketogenic diet is growing and is now increasingly recognized by the clinical community, which provides confidence in the mechanism.

The COVID-19 pandemic meant that Cerecin had to pause its Phase III Alzheimer's trials in 2020. What are your hopes and expectations on when this huge undertaking can begin in earnest?

In 2020 we were gearing up for the Phase III study in terms of establishing CROs, investigators, and the supply chain for investigation materials. Initially, the world thought COVID-19 would be a three-month pandemic, but it has not panned out that way. It may be a long time before we get back to a level of confidence whereby we can run a USD 100 million study of this magnitude. This type of study would not be easy to pause, especially given the possibilities of second waves and mutant strains.

Good management should be able to adapt very quickly – which we did. Additionally, one of the reasons we came to Singapore was to focus our efforts on Australia. Australia is an attractive clinical trials location as an English-speaking country with world-class healthcare, phenomenal

investigators, and supportive government R&D schemes. Australia, today, is also far less affected by the pandemic than many other countries. The situation there has allowed us to go from one study to two, with plans for more later in 2021 and a lot of R&D work around formulation and supply chain scale-up.

We recruited our first executive team member, who is now building our Australian office for exactly these reasons. Australia has served us very well and, handily, is also in a similar time zone to HQ here in Singapore.

Phase III trials can be very capital-intensive, as you have mentioned. What is your funding strategy, and can we expect an IPO from Cerecin at some point?

We are always looking at all available options. Cerecin has been fortunate to get to the stage it is at today through private funding, which is quite unusual. No other company has made it to Phase III trials in Alzheimer's disease without public funding or big pharma partnerships.

The capital necessary to progress to this stage of development generally mean that a company must partner or go public. Cerecin has had big backers behind it with a willingness to invest and the company has not needed to IPO, but there is always value in bringing in new investors. We have regular and ongoing exchanges in various countries; as a US-founded company, we have had conversations with NASDAQ and the New York Stock Exchange, but now that we are in Asia, we are also talking to exchanges in Hong Kong, and Korea.

Currently, we can privately fund our Phase II programs in migraine and infantile spasms. However, if those start to move towards larger pivotal programs, our Alzheimer's Phase III trial launches, and larger follow on studies in Migraine and Infantile Spasms, then we may look to add to our investor base with new private and or public market investors.

To what extent is Singapore still the best place to base this growth story from?

Moving to Singapore was a good decision that has suited the company very well. Every company is different, but from a talent, capital, and raw materials perspective, it still makes sense for Cerecin to be here.

We have been able to recruit a strong team; however, it is worth noting that the Singaporean biotech ecosystem is relatively small. Although there is a good talent pool here in clinical

operations, manufacturing, and supply chain, there are certain roles that are much easier to recruit for in biotech hubs like Boston or the Bay Area.

Cerecin has made substantial progress on the capital side, raising further funds with more pending, based on our programs, that we have been able to source in the region. In terms of manufacturing, we now have partners in Asia and have established an effective supply chain.

The Singaporean government continues to be supportive with increasing investments in high tech innovative industries. It is still early, but there is clearly support for new sources of venture capital. We have been engaged with the government across various channels to feedback and help Singapore grow this important part of their economy.

More broadly, the CNS landscape has also advanced since we last spoke, with aducanumab edging closer to US FDA regulatory approval, potentially representing the first new approval for an Alzheimer's drug since 2003. Does this represent a threat or an opportunity, and what role do you see Cerecin playing in this story?

It is an opportunity. In my last article for PharmaBoardroom, I wrote that CNS could be the next oncology and my belief in that statement is stronger than ever, with an increased interest in CNS and Alzheimer's. The much-discussed "Biogen or aducanumab effect" shows that this has been a tough indication, and what we need to see in Alzheimer's and across the board in CNS is new drugs gaining approval. This will show that trial endpoints are achievable, studies can be successful, and regulators are engaged.

This goes for both the clinical side and the investment side, which is the driving force of this industry – investors need to make money. Investors have lost a lot on CNS, particularly in Alzheimer's, and now need to recoup their losses. Successful studies and approvals have a positive effect across the board; other CNS/Alzheimer's companies that are publicly traded have benefited from this surge of interest with some very successful IPOs and fundraisings last year. For example, Athira, a company in relatively early stages of Alzheimer's drug development, raised almost USD 100 million based on compelling Phase I-II data and then had a very successful IPO in the latter part of 2020, even amidst the COVID pandemic.

Given the company's rapid progression in the past three years and a difficult 2020, what are your hopes for 2021 and in the medium term for Cerecin?

2021 is going to be a crucial year with regards to our two Phase II programs. Our whole team is hunkered down and focused on executing these studies, which will read out in early 2022.

We hope that in 2022 we can then go into a bigger Phase II, III, and potentially even a pivotal migraine study for a drug that will provide a truly compelling treatment option for patients. The progress of Calcitonin gene-related peptide (CGRP) inhibitors for people who live with migraine has been heartening. However, at the same time, there is still a huge subgroup of patients – 30 to 40 percent – who are underserved by those treatments. Alternatives are therefore essential, and *tricaprilin* would be one such option, sitting alongside these complementary mechanisms.

As infantile spasms is an orphan condition, we will hopefully move quickly into the definitive pivotal study after proof of concept is obtained. This means that by 2022, Cerecin could be running a study that would get the company to approval. This would be our first and getting this drug to patients would be hugely impactful and very rewarding to our team. We see this programme as establishing proof of concept in epilepsy, allowing us to go into other orphan seizure disorders or even broader generalized epilepsy, all of which have been shown to be positively impacted by the ketogenic diet.

While there have been challenges, these are exciting times for Cerecin..

What keeps you engaged and excited to be part of the pharmaceutical industry today?

Last year was tough, but for the first time in a long time, the pharmaceutical industry was spoken about as playing a huge role in improving human life.

Unfortunately, the pharmaceutical industry has suffered from a bad reputation for a very long time and our executives tend to be towards the bottom of public opinion rankings. This is hugely disappointing as most of the people I know in this sector are brilliant and well motivated to have impact and help people. It has been heartening to see a more positive public opinion develop around the industry. If we are sensible, the industry will continue to build on that perception.

Hopefully, with that positive public sentiment, there will be increased government support and greater numbers of people wanting to work in this industry, meaning more life changing medicines reaching approval, and more patients being served.

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