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CYDAN: MISSION IN THE ORPHAN SPACE | By W. Koberstein

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THE ENTERPRISERS

Life Science Leadership In Action

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CYDAN: Mission In The Orphan Space

PRIVATE COMPANY

FUNDS RAISED: Cydan I, $16M; Cydan II, $34M

STARTUP DATE: Cydan I, April 2013; Cydan II, September 2017

NUMBER OF EMPLOYEES: 5

FOCUS: Asset-centric strategy, forming multiple spinoffs, each developing a drug for a monogenic rare disease

Orphan drugs have drawn a complex cast of players in the rare-disease therapeutics space. From fired-up parents and advocates, to new companies and business models, all of the stakeholders seem to have vital roles in filling the empty niches of medical need. Cydan created its own new model to answer the business challenge of developing new orphan drugs. Serving as a central hub, the development accelerator finds, selects, and acquires therapeutic candidates, then forms, virtually operates, and ultimately spins off or sells companies, or "NewCos," focused on specific products or product groups.

It has recently closed a new financing for "Cydan II" with $34 million in new capital for de-risking and business development. The experiment was successful enough to produce a $200-million sale of Cydan's first new company, Vtesse, to Sucampo, as well as clinical-development progress of its second company, Imara. Though superficially similar to multi-spinoff organizations such as Velocity, which we examined previously (June 2015), Cydan presents a new and original business model for orphan-drug innovation.

SPLINTERING RISK

Industrywide, much of the total orphan-drug universe has inflated with the proliferation of ever-more precisely targeted cancer drugs. Some new products stretch the definition, and prices, of orphan drugs into outer space — charging 2,000–patient prices in a 200,000-patient market, the highest population allowed for orphan designation under U.S. law. But many companies still dedicate themselves as much to unique "micro-orphan" conditions with tiny patient populations and no viable treatment options. Cydan has recently rededicated itself to creating new companies and products in the defined space of rare monogenetic diseases.

Like other orphan-drug developers, though, Cydan targets diseases that vary from the extremely rare to the exceptionally rampant. Vtesse/Sucampo has a drug in development for Niemann-Pick disease type C (NPC), a disease affecting only about 2,200 people worldwide, whereas Imara is developing a phosphodiesterase-9 (PDE-9) inhibitor, coded IMR-687, for sickle cell disease, which bedevils at least 100,000 patients in the United States and threatens the children of 2 million more people who carry the sickle cell trait. The sickle cell trait may confer some protection against malaria, perhaps explaining why sickle cell disease is concentrated in populations with origins in malaria-prevalent regions. If you are in one of those groups, the disease will not seem rare, but almost common. (See also, "Tackling Sickle Cell" on p. 31.)

It is worth taking a moment to examine Cydan's use of the word *accelerator* rather than the popular term *incubator* to describe itself. The latter implies a deliberate but unhurried process for bringing projects to maturity, but the former emphasizes increasing the speed of maturation for drugs in development. The need for speed illuminates one large avenue for reducing development risk. Speed can be a key advantage for small companies, which have assumed much or perhaps most of the risk in drug development from Big Pharma at this point.

Cydan accelerates development programs, it says, through highly informed candidate selection and fine-tuned therapeutic targeting identified in academic, biotech, and pharmaceutical companies. In the case of Imara, the company drew from a large pool of drugs whose IP it obtained early from the Denmark company Lundbeck. It relies on both internal and external expertise, starting at the top. Co-founder and CEO Chris Adams, Ph.D., was originally a Swiss chemist who since became a veteran of the orphan drug area, mainly on the business side. Adams has driven business development at companies such as Ciba-Geigy, Transkaryotic Therapies, ViaCell, and FoldRx Pharmaceuticals, where he completed an acquisition by Pfizer in 2010. Co-founder and president of R&D James McArthur, Ph.D., is a scientist with a long background in monogenetic diseases at historic companies such as Somatix, Cell Genesys, Phylogix, and Synovex/Adheron. McArthur also serves as Imara's founding CEO.

"Besides rapidly identifying opportunities and advancing them, one thing that has helped us be efficient is having a core team that has broad drug development expertise across late research, early preclinical, late preclinical, and early clinical development," McArthur says. "We also have a group of about a dozen consultants who work with us project after project and are essentially an extension of our team. With Imara, we took IMR-687 from biochemistry to pre-IND (investigational new drug) in 18 months, and now have completed a Phase 1 study in healthy volunteers and will

dose patients in a multinational Phase 2 study within 18 months of that."

The first phase of Cydan's model has produced positive evidence that its approach works well, McArthur believes. Having one drug and company acquired and another on the way in Imara, all in only four years, is an impressive feat by any objective standards.

"We're hoping to do it over and over again on project after project," he says. Late in 2017, the company concluded its "Cydan I" phase, using its internal designation, and marked the beginning of the next round of funding by raising $34 million for "Cydan II."

"Cydan was always designed as a four-year experiment to see whether we could create a more effective, more efficient mechanism for identifying and advancing therapies for rare diseases, so four years was our basic funding cycle," Adams explains. "In some ways like a venture fund, one cycle is closing and we have brought in new money from essentially the same syndicate."

FASTER WITH FRIENDS

Another key factor in speeding Cydan's progress, according to McArthur, has been its close association with a small but strong syndicate of investors, including New Enterprise Associates (NEA), Pfizer Ventures, Lundbeckfonden Ventures, Bay City Capital, and Alexandria Real Estate Investments. The company has advantageously returned to the same set a number of times to finance large steps forward, from its $26-million founding, to the $42-million financing of Vtesse and then the $31-million launch of Imara in 2016. "We have a ready group of investors available to us who are familiar with Cydan, familiar with our efforts, and have become familiar with our projects and de-risking ability. We're ready to apply for that venture capital to advance a drug into drug development," he says. Longitude Capital has joined as an investor in Cydan II.

Cydan was the original idea of Dave Mott, general partner at NEA. McArthur and Adams, introduced to each other by a common friend, began to explore how to translate this idea into a reality. "We discussed how we could find promising therapeutic hypotheses to test and de-risk, then build companies around products and spin them out, find management teams to run and ultimately sell them, and even more importantly, get each product to a place where we could establish human proof-of-concept and confirm the original hypothesis," says Adams.

Once underway, the small Cydan team examined more than 1,000 opportunities, including those from Lundbeck, other companies, and academic and government laboratories. McArthur describes the drill:

"With each compound, we asked, is the underlying science behind the drug compelling enough to take it forward? Will it have a real fundamental impact on the biology of the disease? Do we understand the drug's mechanism of action? Is there a path forward to creating intellectual property around the drug that would make it a compelling clinical and business opportunity?"

During the past five years, Cydan identified more than 60 programs that met the criteria and deserved deeper investigation. It selected 17 assets for de-risking, which it tested for pharmacology, toxicology, clinical development feasibility, manufacturing practicality, and so on, before selecting two products for Series A funding.

The second phase of Cydan will not start the company completely anew; during the past four years of drug and business development activities, Cydan has gained some lasting resources, according to the executives. One they cite consists of the company's close relationships built with patient-advocacy groups and investigators in the orphan disease area. Even though Cydan cannot develop drugs for all of the conditions those stakeholders represent, it can and has helped identify promising therapies for their respective conditions, possibly putting some on the right path to treatment.

Access to capital will offer continuity in Cydan's second stage, according to Adams: "The beauty of our model is we have the capital we need to de-risk projects, and then the same syndicate has the reserves in place to fund the new development. That is the difference between Cydan and other entities such as Velocity." With each project, the company employs what seems to be a modest amount of money up front — in the range of $1.5 to $2.5 million to advance the project to the point of a $30- to $40-million Series A funding — but it also has between $140 and $160 million in reserve to help fund the Series A of each NewCo. "The actual amount depends on the stage of the asset and our goal for human proof of concept. The seamless transition between de-risking and NewCo is a key differentiating feature of Cydan," he says.

RECRUITING FOR TRANSITION

Future projects will add to the time and work Cydan must now spend on current ones, and it is adding people to meet demand. From identifying new opportunities, to de-risking them, to organizing new virtual companies to develop them, the company needs to recruit just the right people to make its model work, and those people must be ready for ongoing change.

"We need people with an entrepreneurial spirit and phenotype, along with the exact expertise to help us make the transition from drugs to new companies," says Adams. "We will bring new people in as members of Cydan, not necessarily as permanent members, but as leaders who will transition out with the assets and

TACKLING SICKLE CELL

James McArthur, cofounder and CEO of Cydan's sickle cell therapy company Imara, explains why and how the company entered the historically futile search for a drug to treat sickle cell anemia, with its PDE-9 inhibitor, coded IMR-687.

MCARTHUR: We had an interest in sickle cell disease because of the tremendous underlying need of patients who live with it. Most people don't appreciate that, even with the best of care today, the average life expectancy of someone with sickle cell disease is only the late 40s. Patients who do live long lives can expect to have damage to the lungs and kidneys, micro-strokes, and for half of the patients, some level of pain from that of an extremely bad bruise to breaking a rib. Because of a publication by a Brazilian group about six years ago, we became interested in phosphodiesterase-9 (PDE-9) as a target for sickle cell. For decades, the only approved therapeutic for the disease was hydroxyurea, an old chemotherapeutic agent. Hydroxyurea is effective in reducing pain and hospitalization and increasing life expectancy, but it is mutagenic, teratogenic, toxic to neutrophils, and should not be taken by women during pregnancy, or while trying to get pregnant by men or women. If we could find a drug that had the same positive effects as hydroxyurea, but none of its negative effects, that would be a very compelling candidate that was already partly de-risked. Hydroxyurea increases the messenger molecule, cyclic guanosine monophosphate (cyclic GMP), inside cells by driving cyclic GMP production. PDE-9 degrades cyclic GMP, so it has the opposite effect and a PDE-9 inhibitor will increase intracellular cyclic GMP levels. That is what made PDE-9 a compelling target. Not only does our drug go after the same biochemical mediator as hydroxyurea, it does so in red and white blood cells, both of which critically participate in sickle cell disease.

We were connected with a Danish pharmaceutical company, Lundbeck, and like many other pharmaceutical companies, Lundbeck had developed PDE-9 inhibitors for neurologic diseases. We asked the company, do you have PDE-9 inhibitors that do not get into the brain? For sickle cell disease, you do not want to inhibit phosphodiesterase-9 in cerebral neurons, but only in the white and red blood cells. Indeed, Lundbeck had hundreds of these molecules that did not get into the brain, and therefore were of no interest to them, but were perfect for us. From the moment we began looking at their molecules, some of which only had the barest of biochemical data, we were able to proceed to a pre-IND for sickle cell disease, building up all the preclinical pharmacology and toxicology data necessary to support the submission, in 18 months. We have now completed studies in healthy volunteers and are dosing our first patient within a few weeks.

become a CEO, CMO, or whatever the role the person is suited for. That is part of the challenge of the transition from being a Cydan accelerator project to it being a Series A funded NewCo. That is one of the lessons we learned in Cydan I."

With Vtesse, Adams says, the transition went well from the get-go. Its future CEO, Ben Machielse, joined Cydan in the de-risking stage with VTS-270 and was still running Vtesse at the time of the Sucampo acquisition. Machielse also worked in the transition at Cydan before his new company launched. "The continuity of leaders in the transition gives us a smooth flow and speed from identification through de-risking and development," adds McArthur.

"One of the advantages is that the leaders are not on their own," he says. "They can continue to leverage the size of the company, and they have the benefit of Chris' expertise in business development and strategy. They have the benefit of my scientific expertise. They have the benefit of medical and development expertise within our company. They will not be standing on the ramparts by themselves, but leveraging our expertise to accelerate the drugs forward."

Cydan recently announced the hiring of Dr. Shi Yin Foo as chief medical officer and Dr. Niels Svenstrup as vice president of development. Overall, say McArthur and Adams, the company is seeking leaders and experts mainly on the science, chemistry, and clinical sides. McArthur says Cydan also will continue doing collaborations with academic centers because of their "extraordinary science," despite the higher costs in time and money they typically require. "We'll be looking for new ideas and ways to help advance tractable projects from these new ideas, though probably the projects themselves will not be coming directly out of academic centers."

STAYING ON TARGET

According to McArthur, Cydan II will stick with the same focus on therapeutic areas as Cydan I — monogenic rare diseases outside of cancer and infectious disease. He says the company now has all of the general and specialized tools it needs to further explore its chosen space:

"We can now leverage the power of rare disease research, where we understand the underlying genetic underpinnings of a disease, the mechanisms of action for drugs that will affect the disease, animal models that can predict whether a drug will have an impact, and biomarkers that indicate whether the drug has target engagement and identify patients who should respond to the therapy. All of that allows us to do focused, smart preclinical and clinical development." (See sidebar, "Orphan Pricing — Cost & Cost-Effective.")

Cydan would like to develop therapies for about 24

ORPHAN PRICING – COST & COST-EFFECTIVE

Any company working in the orphan-drug space may experience the flip side of the patient-community involvement typical with any rare disease. Patient families and advocates often help jumpstart and fuel companies' interest in potential therapeutic approaches and feel a sense of ownership when a company adopts an approach they have advocated. In the case of the Sucampo/Vtesse drug for NPC, one set of parents in particular has recently sued all of the companies involved, claiming the companies will profit immensely from developing a drug identified and refined by the "sweat equity" of the parents and a lone researcher. Before the lawsuit, Chris Adams, Cydan's president, had the following to say about the issue of a drug's price and value once it has been developed and approved for the market.

ADAMS: It is the responsibility of Sucampo (now Mallinckrodt) to finish the current clinical trial with VTS-270 and ultimately determine the value of that therapy. What is the value to the patient group in that patient community and how does that translate to a clinically meaningful outcome for patients? With rare genetic diseases, the value should be based not on extension of life, but on extension of the quality of life. I go back to my roots at Transkaryotic Therapies, where we developed enzyme replacement therapies, which slowed progression of disease for many patients. Potentially, in the future, as we get better and better at understanding the natural course of a given indication, we can then point to the impact on individual patients and more important, what's the impact on the caregiver and outcome. In some diseases such as cystic fibrosis, breakthrough drugs have clearly changed outcomes and extended quality of life. That is where we should focus as an orphan drug industry. Biogen's Spinraza (nusinersen) is a very expensive drug, but has a phenomenal clinical transformative outcome for patients. If we can come up with therapies that perform that well, price is less of a challenge. You still have to defend it with appropriate global value dossiers that demonstrate value. It's not just that it's rare and therefore it's expensive. Some bad-apple companies have repurposed cheap drugs and then packaged them up and tried to sell them at a multiple of what they were originally priced, and that's just not good for anybody, especially not good for the industry. Our job is to develop clinical protocols and clinical data that justifies that value – along with the entire infrastructure that we can provide to parents, caregivers, and patients.

Imara CEO James McArthur added this:

MCARTHUR: If we can make a profound difference to a patient's life that moves them from spending hundreds of thousands of dollars on supportive care or from wheelchair to walking, or blind to seeing – those are the sort of changes that warrant placing a higher value on our product. I've often explained to patient groups, when we look for investment to develop new drugs, we do have to make it a compelling commercial and business model for investors. To put money behind us, they have the right to expect that our drug will have a fundamental impact on the disease and on patients' lives that justifies its price.

specific monogenetic rare diseases, selected by criteria such as extraordinary patient burden, unmet need, relatively empty competitive landscape, good disease mechanism understanding, and predictive animal models. For those diseases, says McArthur, "We attend scientific meetings, talk with the patient organizations, and speak with thought leaders in the field to learn how to identify and advance therapies for these diseases."

In drug modality, the company has learned to narrow its focus. Originally, it looked at gene therapy approaches, but demurred mainly because of cost of entry and the large number of companies already in the field. It also tried screening-based approaches with new technologies or targets, and again shied away because of the time and capital required to take an agent from the bench to the point of a Series A funding round and new company launch.

As time passes and the company progresses, Adams says it accepts an additional role in the orphan space — giving support to other enterprises on the same path. "It is our responsibility to help entrepreneurs who are not quite there yet with their asset, to guide them, to suggest the critical experiments they should do, to help find an investor, and to show them how to get a potential project to a point where it's an investible asset."

Considering the more than 7,000 rare diseases remaining untreated, it is reasonable for a company with an orphan-space mission to help others along the way rather than regard them as competitors. Collaboration for an accelerator like Cydan makes sense at every level. L