ALNYLAM – POISED TO DELIVER ITS BREAKTHROUGH IN 2018

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It was May 2013 when we first wrote about John Maraganore, CEO of Alnylam Pharmaceuticals. Back then we posited that he had navigated Alnylam to the brink of a big breakthrough with its ribonucleic acid interference (RNAi) platform. Considering it is almost five years later, and we have yet to see this "breakthrough," you might be wondering if our definition of "brink" was calculated in dog years. Not quite. As you are well aware, the road to drug discovery and development is lengthy, expensive, and often filled with potholes and roadblocks. Such hazards can delay or prevent a company from ever reaching its aspired destination. For example, this past September a clinical hold was placed on all clinical studies involving fitusiran, Alnylam's investigational RNAi therapeutic targeting antithrombin for the treatment of patients with hemophilia A and B.

JOHN MARAGANORE
CEO, Alnylam Pharmaceuticals

For some people, such adversity could signal the end of the line. Maraganore, however, prefers the philosophy of Friedrich Nietzsche — "That which does not kill us makes us stronger," something Alnylam certainly did in 2017. For example, the company received accelerated assessment (EMA) and Breakthrough Therapy Designations (FDA) for givosiran and patisiran, announced positive Phase 3 data, advanced four programs into late-stage clinical trials, and netted nearly $1 billion through two public offerings.

During this year's annual J.P. Morgan Healthcare Conference in San Francisco, I had the opportunity to sit down with Maraganore. Our conversation covered a wide variety of topics, from the lows of the clinical hold involving fitusiran, to the highs of receiving an FDA Breakthrough Therapy Designation (BTD) a mere two months later for patisiran, Alnylam's investigational RNAi therapeutic targeting transthyretin (TTR) for the treatment of adults with hereditary transthyretin-mediated ATTR amyloidosis (hATTR amyloidosis) with polyneuropathy. In 2018, Alnylam seems poised to deliver its first big breakthrough, and Maraganore is eager to share his perspectives — the good, the bad, and everything in between.

WHAT HAS BEEN THE MOST SIGNIFICANT CHANGE SINCE WE LAST SPOKE IN 2013?

The positive Phase 3 data from our lead program, patisiran, has positioned us from being only R&D to a commercial-stage company in 2018. While a major milestone for Alnylam, it also finally brings RNAi therapeutics to patients. It is one thing to do clinical research and interact with patients enrolled in clinical studies. But you never fulfill your commitment to innovation until you actually bring something to the market. That's what we're about to do, and it's very exciting.

WHAT HAS BEEN THE BIGGEST CHANGE THE COMPANY HAS UNDERGONE SINCE BEING FOUNDED?

Between 2008 and 2012 we conquered the key technical hurdle of delivery for Alnylam's RNAi platform. Had we not succeeded in achieving multiple delivery solutions, we most certainly would be dead as a company. After that it would be the scientific advances that enabled us to execute on development, which has led us to being on the verge of becoming a commercial-stage company.

DID YOU EXPECT THE COMPANY TO HAVE A PRODUCT APPROVED BY NOW?

When we started in 2002, I told investors it would take over a decade and more than $1 billion to make RNAi succeed. If we look at where we are, 15 years since inception and $2.3 billion of invested capital, and the fact that we are about to turn the corner on being commercial, we are pretty much where we're supposed to be.

WAS THERE EVER A TIME WHERE YOU WERE SECOND-GUESSING YOURSELF?

The darkest moment for Alnylam was in late 2010, during the height of the Great Recession. Though internally we were still encouraged by where we believed RNAi therapeutics could go, it seemed as if the outside world had given up hope. Some believed Alnylam already dead. We just hadn't decided to lie down yet. During that dark moment, there was a great article in *The New York Times* written by Andrew Pollack titled "Drugmakers' Fever for the Power of RNA Interference Has Cooled." I still have it in my office as a reminder of the sentiment at the time. People were focused on where Alnylam and RNAi-type therapeutics were, not where they'd eventually be going. It is important to re-

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member how much we were able to achieve in spite of a significant amount of doubt.

WHAT BUSINESS-RELATED CHANGES WERE TRIGGERED BY PATISIRAN RECEIVING ACCELERATED ASSESSMENT AND BREAKTHROUGH THERAPY DESIGNATIONS?

These designations, combined with the positive data, pushed us to ramp up our commercial hiring activities. While we had done some hiring prior to getting the news, now we had to do more at an accelerated rate. Receiving a BTD also changed our thoughts about an approval. Because, although we believed we were on the path to becoming commercial, suddenly we had to consider a much earlier approval date and what would be required to be ready.

TELL US MORE ABOUT "BEING READY."

To have greater control over supply, we're building a manufacturing plant in Norton, MA. It is intended for future manufacturing capacity needs, including serving as a secondary/redundant source to be operationalized in 2019. For the patisiran launch, we are using a third-party, U.S.-based CMO with oligonucleotide manufacturing capability in Colorado (i.e., Agilent). Alnylam already has the ordering infrastructure in place, so we can process orders, deliver drugs, and get paid. We are ready to launch within 48 hours of FDA approval. While we are not prepared to give the exact launch date, I can tell you we are preparing to launch patisiran in the United States sometime in the first half of 2018 (PDUFA date of August 11) and in Europe toward the second half of 2018. We have detailed plans for hiring people, finalizing key capabilities, working with a 3PL, and other important supply chain elements. We have all the necessary state licenses required to be commercial, and we are actively engaged with payers so they know about the disease and aren't surprised when the drug reaches the market. Globally, we will have 250 customer-facing employees, which includes medical affairs, sales, marketing, access, and staff at our patient hub. Our U.S. build is nearly complete, while in Europe we have our headquarters and country managers in place in all major markets. We are currently building up our field force in Germany, as that is the first country where we expect to launch after the U.S. The rest of the commercial build will be staged with regulatory filings. For example, we will be submitting our first regulatory filing in Japan in the middle of 2018. We feel it is important for Alnylam to have its own sales force, as we want to retain significant value and ownership for the products we commercialize. Besides, building a sales force from scratch allows us to craft the type of customer-facing team that can be as innovative of a commercial effort as we have been at R&D.

WHAT BEST BUSINESS PRACTICES HAVE ALLOWED YOU TO BE IN SUCH A POSITION?

We took the business risk that our APOLLO Phase 3 trial results would be positive. This was a huge gamble, as the study was a randomized, double-blinded, placebo-controlled trial involving 225 participants between 24 and 83 years of age, lasting 18 months, and spanning 44 clinical centers in 19 countries. But by taking this approach we were able to proactively complete the chemistry, manufacturing, and controls (CMC) and nonclinical sections of the NDA. In addition, we started a rolling submission just six weeks in advance of the final submission. Our goal was to ensure that the NDA would be in by the end of the year. Moving from the basic science we had back when we started in 2002 to developing a whole new approach for innovative medicines to finally getting one of those medicines through the clinical trial process demonstrates the importance of perseverance and commitment in the drug development process. The fact that it was not easy, combined with Alnylam's near-death moments, makes getting to this point even more rewarding.

TELL US ABOUT THE CLINICAL HOLD ON FITUSIRAN.

Unfortunately, we had a patient pass away who was enrolled in our midstage open-label extension (OLE) study for fitusiran. Although this has always been a potential risk of fitusiran, we hadn't previously seen any specific evidence implicating the compound as being causative. Here's what happened: The patient developed a clot and dosed themself with a replacement factor to treat what they thought was a breakthrough bleed, leading to a thrombotic event. This was misinterpreted by the hospital as a bleeding event, and unfortunately the patient was given more replacement factor to treat the suspected bleed, leading to the patient's further decline and eventual death. At that time, Alnylam made the decision to pause all dosing in all fitusiran studies, so we could look at the entirety of our data to try to understand what happened with this patient. We needed to determine if there was an opportunity for introducing a risk-mitigation strategy that would minimize the likelihood of such an event from ever happening again. We identified a risk-mitigation approach that we believed would be very effective in preserving safety. The FDA (as well as other regulators around the world) agreed, lifting the clinical hold this past December. As such, we have once again started dosing patients on fitusiran.

WERE YOU CONCERNED THAT THIS EVENT MIGHT PREVENT FITUSIRAN FROM BEING DEVELOPED?

Not really, because by this point we had a significant amount of data around fitusiran's therapeutic efficacy. We believed the program had reached a point of equipoise, especially in the high unmet-need hemophilia segment of inhibitor patients. The benefit of fitusiran in getting and achieving hemostasis for those patients without the need for bleeding intermittently and treatment with bypassing agents was really clear.

ANY ADVICE FROM THIS EXPERIENCE TO SHARE WITH OTHER BIOPHARMA EXECUTIVES?

Number one, do what's right for patients, which requires being prepared to pause and assess your situation. Number two, we had to reach out to the community of hemophilia patients and patient advocacy groups to make sure they not only understood what happened, but what we were doing to understand and assess the situation. We were very transparent. And while we did not sugarcoat the situation, we also did not try to make it less of an issue than it was. I was really proud of how our team addressed the situation with patient groups, keeping them informed as to what happened, while also stressing our commitment to bringing this medicine forward, as long as we believed there were good safety thresholds.

WHAT WAS KEY TO BEING PREPARED TO ADDRESS THIS CLINICAL HOLD?

A big part is being extremely efficient with your time and quick to respond. Another important part is being organized and ready. For example, after the event occurred, we had daily 7 a.m. conference calls when a team would go through an action list of items to be worked on. Keep in mind Alnylam was informed about the event on the Thursday before the 2017 Labor Day holiday weekend. Nonetheless, we needed to be ready to make a public announcement the following Thursday. In addition, we had to notify the FDA, the European authorities, and all of our KOLs. We had approximately 30 employees working on it, each with different responsibilities, to make sure we communicated effectively.

YOU COLLABORATE WITH THE MEDICINES COMPANY. HOW DOES THIS COMPARE TO A COLLABORATION INVOLVING A BIG PHARMA?

Last fall we began announcing the results for the APOLLO Phase 3 study of patisiran in hATTR amyloidosis patients with polyneuropathy. Alnylam conducted this study with Sanofi Genzyme. A larger company, by necessity, has a governance process involving a lot more people, thereby taking a bit more time compared to working with The Medicines Company. In my experience, working with a smaller company tends to feel a little less structured, tends to move a little faster, and feels a little easier. But having said that, the relationship we have with Sanofi is very strategic, and we have close and frequent contact with the company's top leadership, including the CEO, Olivier Brandicourt. For example, before APOLLO Phase 3 data was released to the outside world, I called Brandicourt and Elias Zerhouni, Sanofi's president of global R&D, and took them through the data. Despite being at a larger organization with more processes and governance, it is still possible to have very agile communication with senior leadership. This proved extremely important when we had to place a clinical hold on fitusiran, which is also being developed with Sanofi Genzyme.

ALNYLAM'S COLLABORATION WITH SANOFI WAS ORIGINALLY FORMED IN 2014, BUT IT RECENTLY WAS REVISED. WHAT CAN YOU TELL US ABOUT THAT?

Our original agreement pretty much gave Sanofi rights to Alnylam's rare disease pipeline for all territories outside the U.S. We recently restructured that relationship to secure global rights for patisiran and ALN-TTRscO2 (a subcutaneous version of patisiran). In exchange we gave Sanofi global rights for our hemophilia program (i.e., fitusiran), which aligns well considering the recently announced $11.6 billion acquisition of Bioverativ (a hemophilia-focused company). The restructuring of our collaboration with Sanofi is a good example of working closely with a partner to understand what each other's needs are. In this way we were better able to develop win-win solutions. Basically, the leadership teams of our two companies created a foundational agreement during the course of a breakfast meeting, and then our teams went off to finalize the details. We ran into a couple of snags around the relative values of the two different assets and how to best model these, so we came up with a reciprocal royalty program on product sales for ALN-TTRscO2 and fitusiran. L