Aescap 2.0 Company Showcase: Ionis Pharmaceuticals

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Ionis Pharmaceuticals

Founded in 1989 in Carlsbad, California, Ionis Pharmaceuticals is a leading biotech company specialized in the development of RNA-based medicines. The company employs over 800 people and its proprietary technology exploits the so called "antisense oligonucleotide" therapeutic approach. Since inception, the company has heavily invested in R&D to become the leader in RNA therapeutics. Ionis achieved this by constantly challenging itself to allow its technology to reach the full potential it holds.

By today, that technology delivered a blockbuster medicine to treat a neuromuscular disease, called SMA (Spinal Muscular Atrophy), that significantly changed the life of those patients. The product is marketed a top-5 biotech company, called Biogen. The company also brought two other products on the market via a company, called Akcea, of which Ionis owns 75% of shares. Ionis has the broadest and most mature pipeline of RNA medicines, investigating new treatments for many different severe diseases.

Strategy

Originally, Ionis' strategy was to develop medicine candidates until completion of proof of concept, generally being phase II clinical trials. It would then find a license partner that would bear the heaviest financial burden of the last step of clinical development and commercialization. In return Ionis receives milestone and royalty payments. While having secured a large income stream thanks to regular license partners' payments, Ionis recently changed strategy. With the promotion of former COO Brett Monia to CEO, the company announced that in the future it will also bring medicines to the market on its own.

Technology Focus: Antisense Oligonucleotides

The technology Ionis specializes in, antisense oligonucleotides, is one of the therapeutic classes exploiting Ribonucleic Acid (RNA) particles to treat many different diseases. The core mechanism of action of antisense oligonucleotides is to inhibit or modify a part of the messenger RNA (mRNA) that is responsible in the cells for the production of a specific protein. In this way, the antisense oligonucleotide-based medicine can shut down the production of a harmful protein or modify the produced protein in a way that allows for the recovery of an important physiological function. For example, an antisense oligonucleotide medicine can be used to stop or reduce the production of a protein *(figure 1)* that for example would otherwise accumulate in a vital organ causing toxicity, or it can correct the structure of a malformed protein so that it can regain the critical function it normally has in healthy people.

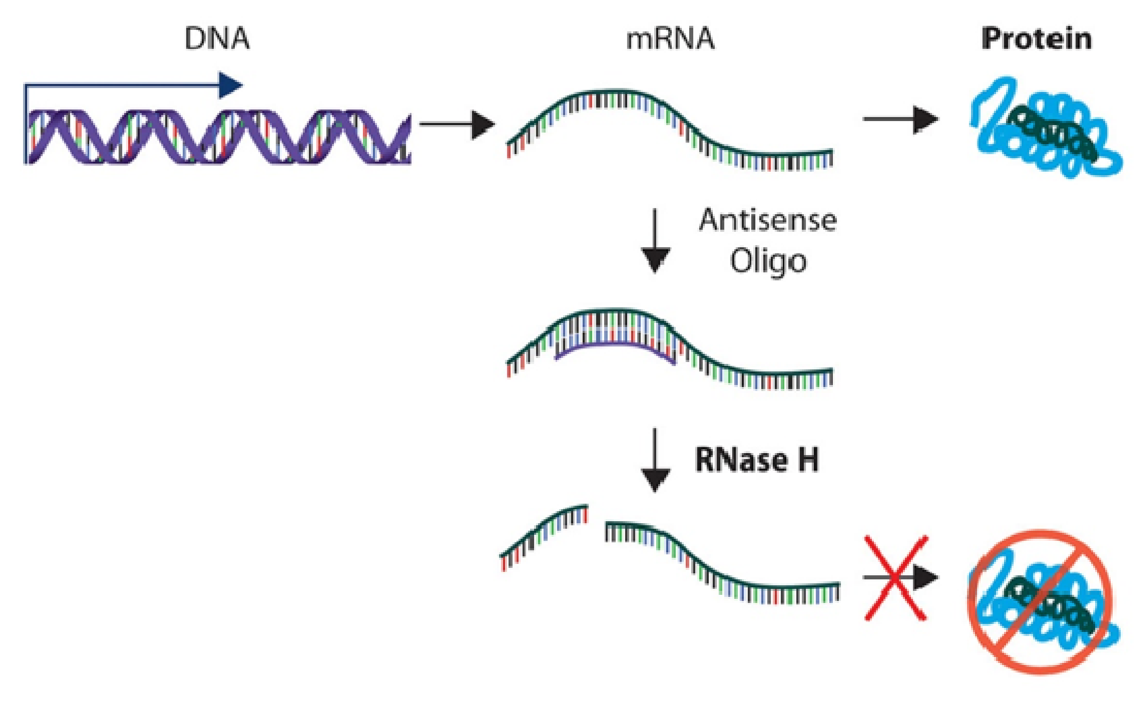

Figure 1. Schematic explanation of how antisense oligonucleotides can stop the production of a harmful protein

RNA-based therapeutics, and antisense oligonucleotides in particular, are so innovative and disruptive compared to 'traditional' medicines because they enable targeting of the genetic root cause of the disease with remarkable specificity, something that traditional small molecules simply cannot do. Thanks to modern sequencing tools, scientists have been able to identify the genetic origin of many diseases, opening the door for the application of therapies like antisense oligonucleotides. There are, of course, limits to the application of these therapeutics. For example, antisense oligonucleotides are unable to cross the barrier - known as the blood-brain barrier - that protects our brain from harmful products. This forces antisense oligonucleotides-based medicines that target the central nervous system to be administered directly into the central nervous system, with unpractical and sometimes even invasive procedures. Of course, when it comes to treating severe and fatal neurological conditions *(figure 2)*, an unpractical administration route is far better than no treatment at all. Moreover, research is underway to surmount this obstacle, like many other barriers were overcome before this.

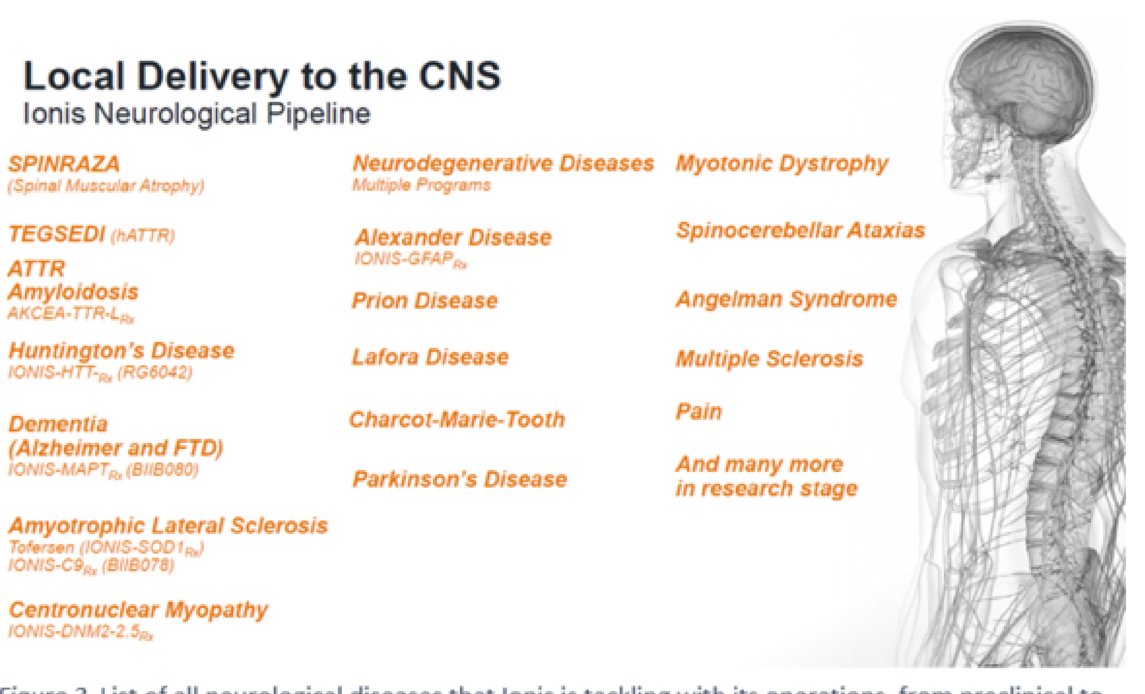

Figure 2. List of all neurological diseases that Ionis is tackling with its operations, from preclinical to commercial stage. CNS: Central Nervous System

Ionis' Technology

Antisense oligonucleotides and their potential in medicine were first discovered over three decades ago, and since then the scientific community has been trying to unravel the therapeutic potential of these compounds. Ionis was then, and still is today, at the forefront of these efforts. Since the company started its operations in 1989, Ionis has constantly invested to improve its technology and ability to continuously incorporate these advancements into the development of better medicines. This allows them to always develop the medicine candidates that bring the most benefit to patients. In this technological journey, Ionis pioneered the characterization of new mechanisms of action that could be exploited via antisense oligonucleotide therapy. This not only enables the targeting of diseases that so far had no treatment available, it also opens new doors to better treatment for well-known diseases such as diabetes and resistant hypertension.

As with all innovation, breakthroughs are only obtained through learning and failures, and Ionis makes no exception. Finally, this has led to the development of successful medicines that are now on the market.

The latest example is a medicine commercialized under the name Spinraza, for the treatment of Spinal Muscular Atrophy (SMA), a group of rare neuromuscular diseases that progressively diminishes the patient's ability to move, and ultimately in the case of children even to breathe. Spinraza is the first RNA-based therapy to reach blockbuster status, defined as reaching at least $ 1 billion in annual sales. Many others are in late stage of clinical development, and they include treatments for devastating neurodegenerative diseases such as Huntington's Disease and Amyotrophic Lateral Sclerosis, commonly referred to as ALS.

Ionis has communicated that it is working to bring forward a technology to enable oral dosing of antisense oligonucleotide medicines, that so far have mainly been administered as injections *(figure 3)*. And this is only one example of Ionis' constant renewal and search for improvement.

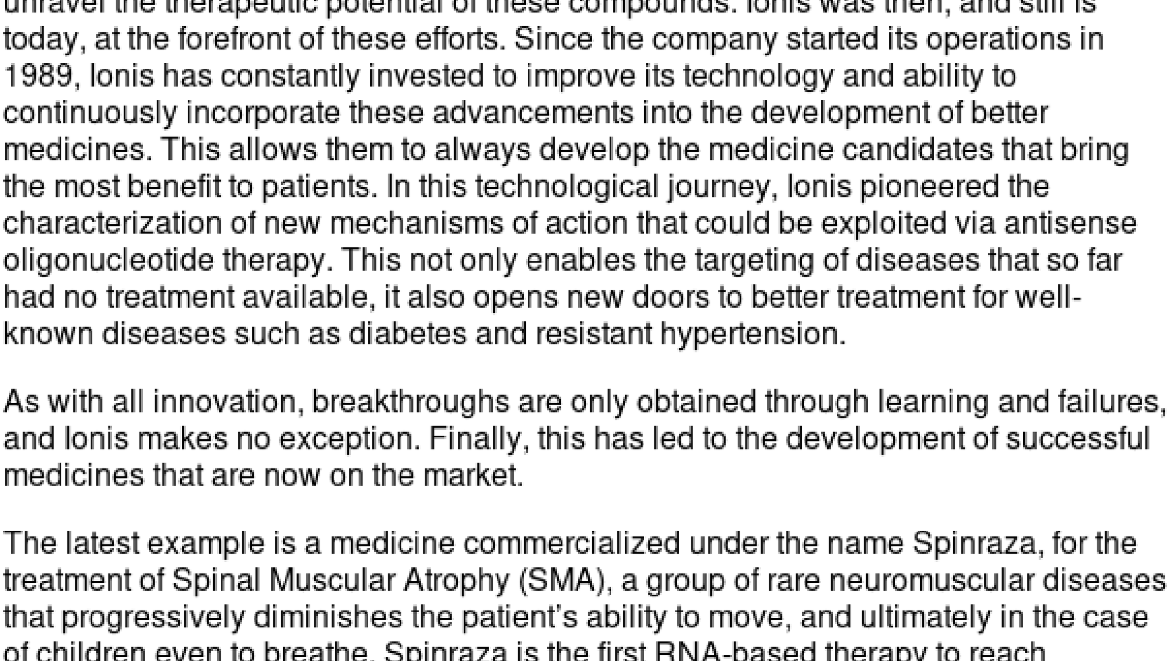

Figure 3. Illustration of the breadth of administration routes and targetable tissues with Ionis' therapeutics. I.V. = Intravenous

From Research to Commercial-Stage Company

Ionis' main business model has been to maintain its focus on R&D, to develop medicine candidates until completion of proof of concept studies, before leaving the last phase of clinical studies and commercialization to a license partner. Validation for Ionis' technology can be found in the list of companies that have decided to in-license products from it. Among others, Biogen, GSK, Novartis, Pfizer and Roche are all biopharma multinationals that have committed serious amounts of money to bring Ionis' medicines to the market, as well as to pay substantial royalties and milestone payments that are typical for this industry.

However, Ionis has taken multiple steps to get closer to bringing their own products to the market. In late 2014, Ionis founded a then fully owned subsidiary called Akcea, that would focus on the late stage development and commercialization of their cardiometabolic products. As progress was made, Ionis decided to take Akcea public in 2017. As of its latest report, Ionis still owns more than 75% of the shares of Akcea, and the latter is commercializing two products originating from Ionis' pipeline in the US and Europe. Akcea represents the first commercial experience for Ionis, but with the recent transition of Brett Monia from COO (Chief Operations Officer) to CEO, the company announced it will transition from an R&D-focused company to a fully integrated biotech company.

Many biotech companies encounter complications when switching from R&D only to a fully integrated commercial organization, but Ionis is well prepared. It plans on undertaking this transition from a solid financial position with a step-wise approach and benefitting from what they learned from the product launches by Akcea and Biogen. Also, Ionis will be able to leverage their significant revenue streams from the many license deals they closed throughout the years to support both research and commercial efforts.

Product Pipeline and Financials

As proof of the broad applicability of antisense technology, Ionis clinical pipeline is divided in 5 different therapeutic areas: Neurology, Cardiometabolic and Renal, Rare Diseases, Oncology, and Other diseases. There are 5 different medicine candidates in phase 3 clinical trials, 20 in phase 2, and 4 in phase 1. On top of that, the company is also pursuing 19 preclinical programs. This is one of the largest clinical pipelines in the biotech industry and is the result of decades of fundamental research on RNA therapeutics *(figure 4)*.

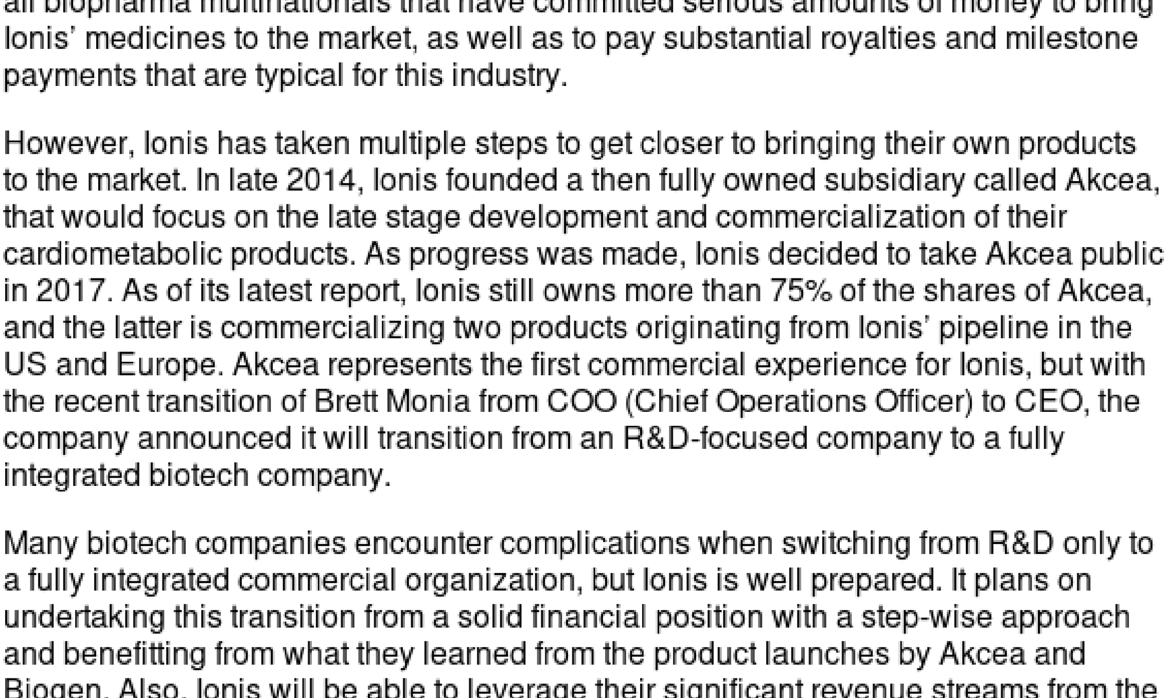

Figure 4. Visual illustration of Ionis' commercial and research pipeline. NDA = New Drug Application, vehicle through which biopharma companies apply for approval to the US Food and Drug Administration (FDA).

Ionis closed 2019 with a cash position of $ 2.5 billion, reporting $ 1.1 billion in revenues and $ 300 million net income for the year. The revenue includes $ 293 million royalties of the blockbuster medicine Spinraza and milestone payments by Ionis' long list of license partners, including Akcea.

Leadership

Ionis Pharmaceuticals was founded in 1989 by Stanley T. Crooke, who led the company as CEO from inception until the end of 2019, and continues to be the company's executive chairman. Prior to this entrepreneurial effort, Dr. Crooke was head of Research & Development departments for large pharma companies such as GlaxoSmithKline and Bristol-Myers Squibb. During his years in the pharma industry he was responsible for the commercialization of tens of medicines, as well as for the clinical development of 20+ more. He received his M.D and Ph.D. degrees at Baylor College of Medicine.

In the late 1980 Dr. Crooke's was an early advocate of the potential of antisense oligonucleotide in medicine, when most scientist saw this technology as a mere laboratory tool. In the 30 years of his tenure, he built and led the company that transformed that idea into concrete clinical benefit for patients. Of course, in doing so he involved many other capable individuals in the company, and in December 2018, Dr. Crooke and the board of directors decided that after three decades it was time for a change in leadership. Effective since January 2020, Dr. Crooke became executive chairman of Ionis' board, leaving the CEO position to the then COO Brett P. Monia.

Though younger than his predecessor, Dr. Monia is a founding member of Ionis pharmaceuticals, contributing both on the technology research as well as clinical development side. Dr. Monia brings years of extensive knowledge in oncology, metabolic diseases, inflammatory disease, neurology, and cardiovascular diseases. Perhaps his most notable contribution to Ionis success, Dr. Monia led the program that yielded the blockbuster medicine Spinraza, a milestone of today's success of the company. Dr. Monia received his Ph.D. in Pharmacology at the University of Pennsylvania and completed his Bachelor degrees in Molecular Biology and Analytical Chemistry at Stockton State College in New Jersey. He is an inventor of more than 100 issued patents and has more than 200 published articles in literature.

With this management change Ionis is transitioning to a commercial-stage biotech company, while keeping the strong R&D fundamentals of the company intact. The new CEO is assisted by several other C-level executives including Chief Corporate Development and Commercial Officer Ms. Onaiza Cadoret-Manier, who has over 25 years of experience leading the sizeable commercial business of Genentech and Pfizer.

Outlook

As it was for antibody-based therapeutics and others before it, biomedical technologies often require decades of research to find viable and effective medical applications. Since its inception in 1989, Ionis has been on the frontline of innovation of antisense oligonucleotides. This Californian biotech leveraged decades of accumulated knowledge and know-how to be on top of the antisense oligonucleotides therapeutic field. We believe the company's highly innovative signature, solid financial position, very broad product pipeline and multiple license deals with top biopharma companies, are going to generate significant value over the coming years.

This is a true high-growth company that would have been acquired years ago if it had not out-licensed most of their products in the past. It is satisfying to see that this strategy has now changed which, together with a nice recent dip in Ionis' share price, triggered us to add it to our portfolio after more than half a year of due diligence.

About Aescap 2.0

Aescap 2.0 is an open-end fund for joint account investing in public biotech companies that develop and market next generation medical treatments. Within its focused portfolio of around 18 companies it diversifies over different diseases, development phases and geographies. Companies are selected for their growth potential ('earning power') and limited risk (technological and financial).

The selection of companies is based on 'high conviction', extensive fundamental analyses combined with intense interaction with management and relevant experts. The fund's performance is fueled by stock picking and an active buy and sell discipline. Biotech stocks are known for their extreme low correlation and high volatility, caused by media, macro-events and short-term speculative investors. This creates an ideal setting for a specialist high conviction fund manager to invest in undervalued companies with a great mid- and long-term earning power. The fund has an average annual net performance target of 20%+ over the mid-term (4-5 years).

Aescap | Science Park 406 | 1098 XH Amsterdam | The Netherlands
Tel. + 31 20 570 29 40 | E-mail: pkrol@aescap.com