Inclisiran’s Interesting Path to Treating LDL Cholesterol

When The Medicines Company licensed inclisiran, they envisioned a drug for the masses that would save the healthcare system money and be reasonably priced for patients. Despite the company having little experience in the oligonucleotide therapeutics field, it went all in on the drug, selling off its other products and downsizing its workforce. It was a gamble, but if successful, it could revolutionize the treatment of heart disease. So, they trusted the science and the story of bringing the drug to market began.

Alnylam and The Medicines Company: a global alliance

Alnylam Pharmaceutical scientists developed inclisiran, and in February 2013, The Medicines Company and Alnylam formed "an exclusive global alliance" to develop, manufacture, and commercialize the drug to treat hypercholesterolemia. The alliance was based on shared values and a commitment to innovation, and as Scott Johnson, vice president of The Medicines Company, explained, it was a logical direction for inclisiran. The Medicines Company was familiar and comfortable in the world of cardiovascular trials, whereas Alnylam’s focus had mainly been in the realm of rare diseases. With The Medicines Company's positive relationship with Alnylam's former CEO, John Maraganore, they were well-positioned and eager to develop the drug further.

Under the agreement, Alnylam would continue the program until Phase I clinical trials were complete. At that point, The Medicines Company was responsible for leading and funding the drug through Phase II onwards, including potential commercialization if the program was successful.

"Now, this exciting collaboration with Alnylam - leaders in their field of RNAi - adds a second potentially disease-modifying approach and more cutting-edge technology to our portfolio," said Clive Meanwell, M.D., Ph.D., Chairman and CEO of The Medicines Company.

The Medicines Company paid $25 million upfront cash to Alnylam, which would continue to receive potential development and commercial milestone payments of up to $180 million and royalties on global product sales of the drug. After licensing the rights to inclisiran, the company set out on its trial program to assess the drug's ability to lower LDL in patients with high levels.

Inclisiran: a Jupiter surrounded by moons

The Medicines Company faced a dilemma once acquiring the drug — do they continue to invest in their other hospital-based drugs or make their sole focus inclisiran?

Inclisiran had the potential to save patients and the healthcare industry a significant amount of money. Yet, "everybody has a plan until they get punched in the mouth," Johnson remarked, explaining that they had a plan until realizing they weren't going to be able to execute it the way they wanted to in order to become profitable.

After plotting out the cost and time to development for each of their products, they used a circle display to indicate the value of each drug, Johnson explained. The circles revealed that inclisiran was a Jupiter surrounded by moons. Even after aggregating the sales of all their other products, they still paled in comparison to the potential success of inclisiran. After meeting with Helen Hobbs of the University of Texas Southwestern, where Johnson describes the science done by Hobbs as "impeccable and elegant," they were confident enough to make a decision.

"We were essentially going to burn the furniture," Johnson said. "We sold every one of those drugs off and raised over a billion dollars over several months."

The Medicines Company was restructured, downsizing from 646 employees in 2015 to only 60. Fortunately, most of the employees that left were salespeople who migrated to wherever the drug was sold.

It was a gamble that paid off, with Johnson describing the Phase II trial results as "spectacular" thanks to the ORION investigators, collaborators, and The Medicines Company steering the ship.

"We had a drug that could potentially treat millions of people, so what went along with that was we better start thinking how to make these drugs cheaper. We're going to have to start

manufacturing at a higher capacity. All of that kicked in as it looked like we were actually going to succeed in the long run," Johnson said.

A drug that could revolutionize heart disease treatment

What made inclisiran unique and worth The Medicines Company selling off all their other products? The drug, now sold under the name Leqvio, reduces low-density lipoprotein cholesterol (LDL), or "bad cholesterol," for people with atherosclerotic cardiovascular disease (ASCVD). However, widely available statins do this too.

A newer class of LDL lowering drugs, called PCSK9 inhibitors, have also been approved. This is significant as not only does PCSK9 limit the effectiveness of statins, but it has also been found that people who struggle with lifelong high cholesterol typically have high PCSK9 levels, while people with lower levels have a reduced risk of heart disease.

While statins are pills, these new drugs are antibodies given via injection. When combined with statins, PCSK9 inhibitors lower LDL levels to as low as 30mg/dL, results unmatched by any other therapy.

Where inclisiran revolutionizes the treatment is its ability as a small interfering RNA (siRNA) to inhibit the translation of the liver protein PCSK9. Additionally, patients only need to receive a dose of inclisiran twice a year, in contrast to the PCSK9 inhibitors that require twice-a-month injections.

"We have seen that PCSK9 gene silencing can substantially reduce LDL-cholesterol in patients, and as epidemiological and disease mechanisms studies suggest, this can further reduce the risks of the world's number one killer, coronary artery disease. Clearly, we see the complementarity of approaches which increase' good cholesterol (HDL-C) and decrease 'bad cholesterol' (LDL-C)," explained Meanwell.

Largest clinical trial for RNAi therapeutics starts

The drug was under the umbrella of Alnylam during the Phase I trials, which revealed that a single intravenous dose resulted in statistically significant reductions of PCSK9 plasma levels of up to 84% and lowering LDL of up to 50%. Inclisiran also demonstrated remarkably low toxicity, only causing mild or moderate adverse reactions at the injection site. Following the success of the Phase I trials, it was now up to the Medicines Company to lead and fund the drug through its next phases, and the ORION clinical program was launched in 2015.

In 2019, The Medicines Company announced that Inclisiran hit its primary and secondary endpoints in its ORION-10 Phase 3 trial, which tracked patients' LDL levels for 18 months following the start of treatment. The findings revealed that the drug was more effective at lowering LDL than statins and showed a placebo adjusted 58% decrease in LDL at day 510.

The drug's effectiveness was studied in three randomized, double-blind, placebo-controlled programs — ORION-9, -10, and -11 clinical trials. All enrolled participants, 3,457 adults with HeFH or clinical ASCVD, were taking the maximum tolerated statin therapy but required additional LDL lowering due to their risk of cardiovascular events. The studies found the inclisiran group had a change in LDL baseline levels of 45.8% by day 510, whereas the placebo group had a 4% change (1). This comprehensive Phase 3 program is considered the largest clinical program conducted for an investigational RNAi therapeutic program.

The gamble pays off: Novartis acquires inclisiran

Since acquiring licensing rights for inclisiran, Johnson said there was distinct but guarded interest from most major pharmaceutical companies throughout the years. In 2020, a week after announcing positive results for ORION-10, the second of three 19-month Phase III trials, Novartis announced it was acquiring The Medicines Company for $9.7 billion and would obtain the global rights to develop, manufacture, and commercialize inclisiran under a license and in collaboration with Alnylam Pharmaceuticals (1).

"We are excited about entering into an agreement to acquire The Medicines Company as inclisiran is a potentially transformational medicine that reimagines the treatment of atherosclerotic heart disease and familial hypercholesterolemia," said Vas Narasimhan, CEO of Novartis.

Describing the drug as a "revolutionary approach" to treating heart disease, he added that he believed the drug could significantly contribute to improved patient outcomes and help healthcare systems address cardiovascular disease, the leading cause of death globally.

Promising trial results lead to approval

In December 2020, based on the promising results of the ORION clinical trial, inclisiran received its first approval in the European Union for use in adults with primary hypercholesterolemia (1). For the drugs U.K. launch, Novartis partnered with Britain's NHS to identify people at risk of heart disease who did not respond to statins.

Approval in the United States wasn't as certain, with COVID-19 travel restrictions preventing the FDA from sending a third party to inspect the facility. However, the FDA noted no concerns about inclisiran's efficacy or safety, and a year later, in December 2021, it received FDA approval.

As our OTS president, David Corey, PhD wrote, inclisiran has the exciting distinction of being among the first oligonucleotide drugs to be advertised to the general population in a mass-market television commercial.

Inclisiran: a drug for the masses?

With FDA approval obtained, the history of previous PCSK9 inhibitors — Praluent and Repatha, PCSK9 antibodies — still cast a skeptical shadow on the drug's success. The high price point of these drugs made it difficult for patients to access them, and insurance companies were reluctant to reimburse for them. The companies eventually yielded to market pressure and dropped the drug prices, with Repatha dropping from its initial $14,000 a year price to around $4,500 to $6,600 and Praluent dropping to $5,850 a year.

The clinical trials demonstrated that inclisiran lowered LDL to the same extent as Repatha and Praluent. However, in contrast to its PCSK9 competitors that require doses twice a month, inclisiran only requires doses two times a year. The less frequent injection schedule could save the healthcare system significant money by cutting it from 24 doses at a doctor's office a year to only two. But The Medicines Company hoped for more. Meanwell wanted inclisiran to be affordable for the people who needed it; he hoped the fewer doses and lower cost would make it the clear choice.

Novartis's vision for the drug differed. Priced at $3,250 a dose and given that patients need three doses in the first year followed by two doses each subsequent year, this equates to $9,750 in year one and $6,500 every year after — higher than Praluent and Repatha and not exactly priced as a drug for the masses. However, Novartis has emphasized reimbursement and access to inclisiran, offering zero copays for the commercial population, leaving only those on Medicare Advantage plans without the out-of-pocket benefit.

Inclisiran: a story that's still being written

The story of inclisiran, sold under the market name Leqvio, continues to be written. Its early chapters were filled with hope and suspense, which included teamwork between two companies that saw its potential and risky moments of betting it all. As heart disease remains the leading cause of death worldwide, its following chapters will hopefully be filled with patient success stories and an achievement of being accessible for those who need it.

References

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