

Jean-Paul Clozel - CEO, Idorsia



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In an exclusive interview, Jean-Paul Clozel explains Idorsia's unique value proposition as a biotech focused on small molecules, how agnosticism in terms of therapeutic areas leads to more innovative medical breakthroughs, and why scientific innovation continues to motivate him.

Last week, you returned to the JP Morgan conference for the first time as CEO of Idorsia. What was the message you wanted to convey about the company and how was it received?

Our main goal was to explain the vision for the company. Analysts and investors will focus on our product pipeline etc, but we wanted to highlight how we are aiming - and are on a good track - to become a mid-sized pharma company.

What is unique is our vision to build a sustainable company; we do not want to be acquired or necessarily make fast returns. We are not a puppet in the hands of a few investors, but rather a company with strong and stable stakeholders such as J&J, myself, and my wife. We are in a very fortunate position to be able to plan for the future and explain what is needed to become such an independent, innovation-driven and yet financially sustainable company.

Idorsia is somewhat unusual as a biotech with a focus on small molecules. This sounds almost counter intuitive in a world driven mostly by large molecules. What is the rationale behind this focus?

When you have started two companies, people think that you like risk. In fact, I hate risk and have tried to avoid it my entire life. One big risk is technological. New technologies – although antibodies are no longer very new – are inherently risky. From seeing cell and gene therapy as something of a home run, people are now waking up to the fact that it is not so easy.

Therefore, I like using very established technology: small molecules. Here in Switzerland, we are in close proximity to very relevant universities that compete with the best in the world training talented chemists, which we employ and leverage for our scientific and clinical work.

There are so many things that small molecules can do that other technologies cannot. It is great to use mRNA technology for a vaccine, but it is not appropriate to use injectables for sleep drugs, for example. We try to look at diseases which can only be addressed through small molecules – of which there are many – and we are doing very well. I want Idorsia to become the best small molecule company in the world.

We are not averse to new technology – indeed, we are using CRISPR in our research – but in the end we want to make therapeutics on the basis of small molecules. We are leaving areas like gene therapy to other, highly specialised, companies.

Given your long experience in research and development, what kind of incremental improvements have you implemented to help reduce risk?

The uptake of new technologies can lead to incremental improvements. For example, robotics can help with high throughput screening, which allows us to use the very rich and interesting library of small molecules that we have accumulated over 20 years of doing chemistry.

Secondly, we use artificial intelligence (AI) to interpret data and it is now possible with computers to obtain the 3D molecular structure of proteins. Many technologies, when combined with molecular organic chemistry and small molecules, can really improve our output.

Of course, as many new targets are discovered every day, sometimes an antibody is the quickest and most efficient treatment, but there are often advantages to using existing and small molecule drugs. It is always more convenient for the patient to take a drug orally once a day rather than go

to a hospital for an infusion.

Regulators like the FDA are aware of the increasing cost of R&D but are rather cautious about the true impact of AI on costs and speed. During an exclusive interview we conducted a year ago, they told us that it is being used as an excuse by companies trying to find a narrative for the R&D hurdles they are facing. What do you think?

While we believe that these tools really do help, and are already helping, we are still at a testing phase and there is a long way to go. Many companies say they are doing AI but are having a negligible impact. There is a need to partner with excellent companies testing mesmerizing new tools.

Additionally, the regulatory authorities are demanding more and more answer around issues like toxicology and quality assurance, which cost more and more to perform. Therefore, while on one side commoditized tools which decrease research and development costs are increasingly becoming available, on the other side, the regulatory requests for more information are driving costs higher. My point is not that these requests are wrong; simply that regulatory bodies like the FDA and EMA are looking to cover more issues and prevent adverse effects as the science itself evolves. Because of this, the cost of developing compounds will increase, but time to market will not accelerate. Regardless, tools like AI remain interesting and they broaden our understanding.

With a portfolio of 12 drugs in clinical development today, how have you chosen the therapeutic areas to target and where is there operational leverage?

We have around 25 projects in drug discovery, 12 in clinical development, and every year we are discovering new products. Our focus tends to be on cardiovascular, immunology, and CNS with sleep and psychiatric indications.

However, when you discover a very interesting new molecule and believe it can make a change, it is very difficult to predict exactly which disease is going to be impacted. At the beginning, you may discover a receptor antagonist without knowing which role this receptor plays in physiology or pathology.

In some big companies, if that receptor does not play a role in a disease area where they are active in terms of marketing, the molecule is viewed to be deviating from the company strategy and thus

is stopped in its development. However, at Idorsia we do things differently; our attitude is to see how we can adapt the marketing organization to the product and, if it is very innovative, there is no reason why we should not develop it.

Marketing uses tools which are common to every type of product; a commercial group technically can sell anything. Moreover, the industry has changed and there is no longer a need for thousands-strong armies of medical representatives, as was the case a few years ago, to be successful. Today, digitization makes medical professionals and patients more accessible. By harnessing tools that access social media networks and online communities with good PR, companies can sell drugs with a much leaner infrastructure. Therefore, we will be able to quickly adapt to different therapeutic areas when we find a very innovative product.

Of course, that means we rely on innovation and not me-too products, that are neither the best-in-class nor the first-to-market. If a small company like Idorsia were introducing the number three or four product with any clear differentiation against a big company like Pfizer, Roche, or Novartis, we would have no chance. However, if we can bring very good products to market which are the first in a new category, we can achieve great commercial success.

How does this mix of therapeutic areas impact the clarity of the storytelling around Idorsia you are able to give to investors?

We are a company based on innovation. Innovation can happen at any time and we must be both open to and ready for it. As you know fortune seeks the prepared mind. With this mindset and an accompanying infrastructure, when serendipity strikes and we make a break-through discovery, we will be able to exploit it. Christopher Columbus set out to go to India but ended up discovering America. We cannot neglect the fact that he discovered America, but it was not his primary endpoint.

The same is true of a lot of discovery. For example, Moderna never had COVID-19 in its business plan but was ready and able to pivot to develop and produce a vaccine to protect from the SARS-Cov-2 virus. In a company like ours, where incredible discoveries are made every week, I do not want to limit their impact by pigeonholing our strategy into specific therapeutic areas.

This is possibly a problem of management, where many managers – in order to give themselves a reason to exist – state that their company is only operating in a specific therapeutic area. This strategy is easy to explain to investors and gives the impression of focus, but if the company then

does not discover a drug within those boundaries, they have nothing to sell.

In the current structure of Idorsia, does Janssen have the first right of refusal, does it depend on the candidate, or is the arrangement something different?

Janssen only has the commercial rights for one of our products apocitentan, for patients with difficult-to-treat hypertension. For all other products, we are free to do what we want, free to co-commercialise with other players or we can do it ourselves. For instance, we are going to sell our sleep drug ourselves with help from Syneos in the US, or Mochida in Japan.

Idorsia's insomnia drug will certainly not be the first on the market to claim to have an impact on this disorder. How will you convince HTA bodies and payers of its innovativeness?

I can draw an analogy with the car industry. For 100 years, these have been vehicles with four wheels going from A to B. However, the performances and designs have changed dramatically, so much that the final product still has four wheels but is now completely different.

For the last 20 or 30 years, there have been no big discoveries in insomnia, but our drug has a new mechanism whereby the patient is not put to sleep but prevented from being awake; something very different. To take away the alarm clock is not the same as a sleeping pill.

All existing drugs up to the discovery of the orexin receptor antagonist were anaesthetics which decreased the function of the brain, caused memory loss, and did not lead to natural sleep. During the night, patients taking these anaesthetics could lose control of the brain, which led to complex behaviours.

Our receptor antagonist, on the other hand, takes away the mechanism which wakes a patient up, or which keeps them awake when the system is over-stimulated. That represents a big advantage in that when the patient wakes up, they will be in good shape and will have had natural sleep.

The problem was to find a drug with the ideal pharmacokinetics. We will not be the first to launch an orexin receptor antagonist. But we potentially have the best. Let me explain: obviously, it is nice to say, "you don't wake up", but if the drug works until midday the next day, there is a big issue! It took us 20 years to find the ideal drug which would work quickly but not for too long. A drug with a digital activity for a digital world. The unique properties of this drug mean that patients sleep well

and function better the following day, with a better mood and memory, with a benign adverse events profile. Very few people realize how much of a revolution this is.

What other product from Idorsia's pipeline are you most excited about?

That is like asking me if I prefer my father or my mother! I am excited about all of them for very different reasons. Our drug for subarachnoid haemorrhage is very encouraging and could help with what is a very bad disease. It mostly affects younger women, who get a cerebral haemorrhage. After the repair of the bloodloss there is a risk of cerebral spasms leading to terrible brain damage, and a huge impact on quality of life.

A very good friend of mine got an aneurysm at medical school and 40 years later he still cannot move his right arm and is tremendously handicapped. This incited me to see if we could do something to really help these types of patients. We got some very good results from our studies in Japan and are hoping to launch there next year.

We also have a tremendous program for treating resistant hypertension for which the commercial rights belong to J&J. Patients suffering from this form of hypertension are frequently in the African American population and it is very difficult to treat, representing a huge medical problem. We are in the process of finishing our patient recruitment, next year we will get the results, and eventually we expect to have an enormous impact on this therapeutic area.

**Are you agnostic in terms of how your drugs will be priced when they enter the market?
How does it diverge from chronic diseases to rare and ultra-rare diseases?**

Not at all, I have a very clear view on prices and think they must be reasonable. The pharma industry is sometimes excessive, and some prices today are out of control and just do not make sense. Prices have to make sense and correspond to the patient benefit. Companies making drugs that treat 500 patients cannot expect the same revenues than if they are treating five million.

We need to revert back to reality and focus more public health

I am not a pricing specialist, but as a medical doctor I believe public health is very important. Public healthcare spending cannot be reserved for ten percent of the population while 90 percent do not get the right drugs. This is where the excess' are unfolding their biggest challenge. It is becoming

more and more difficult to discover, develop, and sell drugs if they serve millions, because there is a reluctance to pay, but it is where most would benefit. However, there is a willingness to pay if the drugs serve 4,000 or 5,000.

Of course, in the past the opposite was true. At one stage, 20 or 30 years ago, if you suffered from a disease that only affected a few thousand people, no drugs were being developed because there was no incentive in terms of potential revenue generation. Regulation changed and incentivized the pharmaceutical industry to produce products to help patients with rare disease. The pendulum swung into the other extreme, to the extent that barely any new treatments for broad indications are being developed. We need to revert back to reality and focus more public health.

To what extent has COVID-19 turned the spotlight on this key issue of public health once again?

COVID-19 has led to a re-evaluation of the importance of infectious disease research; a field where few companies were working and where many had given up on vaccines and antibiotics. Public health issues were being forgotten.

What impact has the pandemic had on Idorsia and the ability of its R&D team to continue to be collaborative and creative?

Those working on research and discovery are less impacted. By definition, there are very strict safety and sterility norms in the labs and those working on cells in these environments have always been wearing masks. The tasks that could be done off-site needed to be defined, and home-office has been implemented for these tasks.

A bigger impact has been on our employees in clinical development. Hospitals have become more difficult to access, but new techniques have been developed, such as making video calls with patients and measuring the blood pressure of resistant hypertension patients with an automatic device. There have been some positive changes brought about by the COVID crisis.

Besides the impact to our processes, some of the products we are developing are also especially relevant in this period. Our autoinjector for myocardial infarctions (MIs) allows patients to simply inject themselves once they suspect an MI and receive protection for four hours, during which time they can go to the hospital to get treated. Getting an ambulance in crowded metropolitan area like

New York has been very difficult in the past 10 months, with all ambulances being taken up by COVID patients and needing to be thoroughly cleaned between patient transports. Therefore, a patient with an MI in such a city might have to wait hours for an ambulance, by which time it might be too late for help.

We are currently launching the Phase III clinical program for this compound, but I am hopeful for its outcome. The device is mostly for people who have already suffered of a first MI, are at risk of having another, and who know what one feels like. To ease fears that using the autoinjector could cause pain, at the beginning of the study the participants inject themselves with a placebo and therefore, if and when an MI occurs, they will not be afraid of injecting themselves.

In 2020 Idorsia invested a significant amount - CHF 300 million - on R&D up until September. Is this level of spending likely to continue or is it a consequence of a pre-planned fast-track strategy?

Idorsia is a ten-to-15-year story condensed into just three years. We are discussing the launch of a drug three years after its creation; something unheard of in the life of a biotech which usually take more than ten years to get to the market.

We are closer and closer to becoming profitable and revenues will likely start as soon as this year as we get royalties from J&J for ponesimod once hopefully approved later in March. As we launch more drugs, other sources of revenue will come in and we are confident that they will be large.

Why did you decide to list the company on the SIX Swiss Exchange rather than on the NASDAQ?

At Actelion, our strategy was based around the idea that it was better to be a big fish in a small pond than a small fish in a big pond. Although Switzerland has a good reputation as a pharma hub, biotech is predominantly a US business, so being quoted on the Swiss market made us the exception and differentiated us. There are plenty of biotech companies listed in the US, while only two or three were listed in Switzerland.

However, we continue to evaluate the best option for the future. COVID-19 and the rapid development of a vaccine has made people realise that biotech is the technology of the future and essential not just to health but also economies.

What continues to appeal to you about managing a company directly as CEO, given your long experience in similar roles and passion for R&D?

If I was the CEO of a large company, I would have given up a long time ago! What drives me more than anything is innovation and the projects. As a cardiologist, if I can change the lives of millions of people with MI, what could be better? Moreover, our sleeping pills can change the lives of patients that sleep on average only three or four hours per night; this is a huge motivator. Scientific innovation is what drives me and, as I am in good health, why would I give up on such an exciting journey? I, along with my wife Martine – our CSO – am here to help the scientists and work together with them. This is our passion.

How would you characterise Idorsia's commitment to diversity and gender equality, given that the only woman present on your management team is your wife?

The ratio of men to women within the company as a whole is around 50-50 and we have a lot of women in key positions. The pharma industry changes slowly. If you want leaders that grow in their roles as scientific experts, then you need to let them gain experience, which takes time. Hence under the visible leadership level, our heads of toxicology, drug regulatory affairs, clinical operations, global marketing, Idorsia US etc. are all women. We are committed to equality. However, I am not looking to have positive discrimination; I want people in positions not because of their gender, but their ability and competence.

We are living in incredible times, what do you hope will change in our industry over the next few years?

The most important thing is public health. Although there has been a huge rush to invest in rare and ultra-rare diseases and cancer, the biggest killer is still cardiovascular disease. Without investment into research in underfunded areas like cardiovascular, antibiotics, and psychiatric diseases – as well as a regulatory framework that incentivizes it – life expectancy and public health will retract as you can already see in the US now.

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