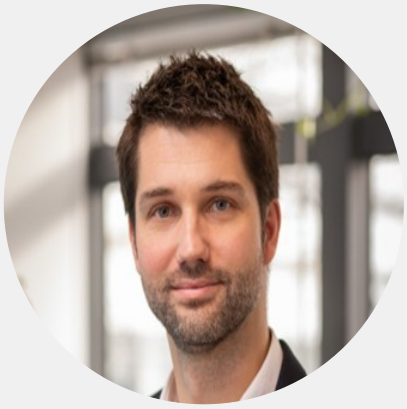
Jean-Baptiste Caquelin – Country Manager, Alnylam France



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Alnylam is reshaping therapeutic possibilities through RNA interference, and France has become one of the strategic environments where this shift is most visible. In this interview, Jean-Baptiste Caquelin reflects on the scientific foundations of RNAi, the strengths and pressures of the French rare-disease ecosystem, and the conditions needed to ensure that breakthrough therapies reach patients without delay. His perspective combines scientific conviction with a clear view of France's role in advancing the next wave of innovation.

What path led you into rare diseases and eventually to Alnylam France?

I trained as a pharmacist and chose early on to pursue a career in industry, attracted by the possibility of working at the intersection of science, medicine and strategy. After growing up in eastern France, I moved to Paris to complete a specialised master's degree in health marketing at HEC Paris. That programme opened doors to several organisations of different sizes and cultures, including Servier in neurology and Boehringer Ingelheim France in cardiology and thrombosis. My real entry into rare diseases came when I joined Shire France as product manager in hereditary angioedema. At the time, I knew little about the field, but I quickly became drawn to an ecosystem where laboratories, clinicians, patient associations and reference centres work side by side to improve care.

France’s rare disease framework shaped much of what followed. The twenty-three national Rare Disease Health Networks (Filières de Santé Maladies Rares, FSMR) coordinate the network of reference centres (CRMR) and competence centres (CCMR) across the country. This structure creates coherent pathways, supports multidisciplinary expertise and enables earlier identification of patients, although diagnostic delay remains a persistent challenge. Working within this coordinated environment gave real meaning to my work and showed me how the right structure can change the trajectory of patients who often face years of uncertainty before receiving a diagnosis.

Over nearly eight years at Shire, I moved from marketing roles into field leadership, which brought me closer to clinical reality and deepened my understanding of how physicians manage rare conditions in everyday practice. I was leading teams across several therapeutic areas when a former colleague, who had just been appointed to build Alnylam France, encouraged me to consider joining the new affiliate. I still remember that call. Within days, I met the team, explored RNA interference (RNAi) in depth, and realised how transformative a technology could be if it addressed disease mechanisms directly and offered options where none existed. The scientific foundations were compelling, but so was the sense of building something new from the ground up.

When I joined, Alnylam France was still a founding team working out of a flexible Regus office in Paris. We had just reported phase 3 results for our first product, and the European marketing authorisation (AMM) followed shortly afterwards, while France had already granted early access through an ATU. It was an entrepreneurial moment where almost everything had to be created, not only in France but across Europe as the organisation expanded. Alnylam’s origins as a research-driven US platform and its choice to remain independent were rooted in a clear conviction: a breakthrough therapeutic class like RNAi cannot remain confined to one geography. Patients everywhere should be able to benefit from its potential, and building European affiliates was essential to making that ambition real.

How do you explain RNA interference as a therapeutic approach, and what distinguishes it from other gene-silencing modalities?

RNA interference, or RNAi, is a natural mechanism that cells use to regulate the production of proteins. It relies on small interfering RNA, known as siRNA, which recognises a specific messenger RNA (mRNA) and triggers its degradation. Once the mRNA disappears, the corresponding protein is no longer produced. This principle, described in 1998 and later recognised by a Nobel Prize,

provided the scientific foundation on which Alnylam was created in 2002. Turning this mechanism into medicines required more than a decade of research, particularly to solve the question of safe and precise delivery into human cells. Many organisations explored the field before stepping away because the technical hurdles were considerable. Alnylam continued to advance the science until the first RNAi treatment was approved in 2018.

RNAi shares a similar ambition with antisense oligonucleotides. Both aim to silence a disease-driving gene by preventing the production of a harmful protein, yet they rely on distinct biological processes. These differences can influence the efficacy and safety of these therapeutics, their specificity toward a target cell, or the duration of the therapeutic effect

The real strength of RNAi lies in its precision and in the possibility of designing siRNA against a wide range of targets. To date, we have targeted delivery of RNAi to the liver and central nervous system, with ambitious expansion plans to address all major organ systems by 2030. The technology’s potential extends across multiple therapeutic areas because, theoretically, Alnylam can silence any gene within the human genome

Delivery remains one of the main challenges, and this is where Alnylam has concentrated much of its innovation. Advances in chemistry and conjugation, especially GalNAc-based delivery to hepatocytes, have allowed us to reach the liver with high specificity and a prolonged duration of action.

By acting directly at the source of disease biology instead of managing downstream symptoms, RNAi has the potential to transform the management of both rare and more prevalent disorders.

How did French clinical expertise support the emergence of RNAi therapies, and how did regulators approach the evaluation of this new class?

French centres played a decisive role in the early development of RNAi therapies. Several expert sites, including those within the FILNEMUS neuromuscular disease network, took part in the first phases of the clinical programme. These centres of excellence contributed to trial design, patient identification and data interpretation in the transthyretin amyloidosis studies. France was the leading recruiting country in Europe in our first phase 3, and the phase 3 results were presented there at the global level. This demonstrated to the scientific community that RNAi has now become an effective and safe therapeutic class, offering hope for individuals and families facing progressive diseases and lacking effective treatments. This early involvement helped shape the scientific

understanding of the technology.

As with any new therapeutic class, regulators paid close attention to questions of safety, specificity and long-term effects. A central point was distinguishing RNAi from gene therapy. RNAi does not modify DNA and does not act on the genome. It targets mRNA only, which makes the effect reversible and helps ensure specificity without off-target DNA changes. More than a decade of accumulated data supported this evaluation, and the participation of French patients provided additional clinical insight and real-world observations for the Haute Autorité de Santé.

Confidence in RNAi grew in parallel with improvements in delivery. Our first product required an intravenous infusion every three weeks. Over successive generations of chemistry and vector design, administration schedules have shifted to monthly, quarterly or even twice-yearly dosing depending on the indication. These advances show how innovation in delivery directly translates into a better therapeutic experience and, ultimately, a broader clinical impact. France’s structured rare disease ecosystem, its strong network of expert centres and its early engagement in clinical research positioned the country as a natural partner in the development of RNAi. This collaboration has supported both scientific progress and continues to anchor France as one of the key contributors to the evolution of this new therapeutic class.

How would you characterise Alnylam’s current therapeutic footprint in France and the strategic importance of the country within your broader European landscape?

We now have four RNA interference therapies authorised in Europe and gradually established in France. Patisiran and Vutrisiran both address transthyretin amyloidosis, and vutrisiran recently received European approval for adults with cardiomyopathy linked to the disease, whether hereditary or wild-type. Givosiran is indicated for acute hepatic porphyria, a severe rare condition defined by recurrent abdominal attacks and neurovisceral symptoms. Lumasiran treats primary hyperoxaluria type 1, a metabolic disorder affecting children and adults that can rapidly lead to kidney failure and for which no therapeutic option previously existed.

France played an important role in facilitating early access to these therapies. Lumasiran, for instance, received nominative early access at the end of 2019, followed by a cohort early access authorisation in November 2020, with the first inclusion recorded that same day. For patients and families confronted with this condition, the arrival of a first-in-class treatment marked a significant change in the care pathway.

Our portfolio spans different levels of therapeutic focus. Givosiran and lumasiran each silence a single disease-driving mRNA, while transthyretin amyloidosis exists in both hereditary and wild-type forms but shares the same underlying transthyretin pathway. As our amyloidosis portfolio now also covers the cardiac indication with vutrisiran, we continue to work closely with the authorities to enable access as quickly and as consistently as possible.

France occupies a central place for us because of the depth of its rare disease ecosystem. The network of reference centres, combined with highly structured care pathways, enables early identification of eligible patients and supports robust participation in clinical research. As a result, France consistently ranks among the leading contributors in Europe across hereditary amyloidosis, acute hepatic porphyria and primary hyperoxaluria type 1. This ecosystem lets us run studies with clarity and speed, which improves how we evaluate and refine our treatments.

What strengths define France’s rare disease ecosystem today, and where do you see room for adaptation to maintain its leadership?

France has developed a rare disease ecosystem that remains a benchmark internationally, largely because it brings together reference centres, competence centres, diagnostic laboratories and patient associations within the national Rare Disease Health Networks (Filières de Santé Maladies Rares). Networks such as FILNEMUS for neuromuscular disorders and CARDIOGEN for hereditary cardiac diseases give the country a coherent structure that ensures patients can access specialised expertise without travelling long distances. This coordinated approach also improves early identification, which is critical in rare diseases where symptoms are often subtle and easily confused with more common conditions. Over time, it has allowed France to build well-characterised patient cohorts that support scientific research, clinical trials and the evaluation of innovative therapies.

Looking to the future, several developments will be important. Genomic platforms are expanding, and France is now accelerating efforts in newborn genetic screening and the integration of artificial intelligence to refine diagnostic pathways. The early access framework is another key asset, since it enables patients to receive innovative therapies before full reimbursement, although recent complexities highlight the need to strengthen its long-term sustainability.

The main challenge lies in access timelines. The period between a European marketing authorisation and full reimbursement still averages more than 500 days in France, whereas countries like Germany grant access within a much shorter timeframe. The role of the French

authorities remains essential, but the overall evaluation and regulation processes need to become more efficient so that avoidable delays do not hold back access for patients who often face severe and rapidly progressing diseases. Preserving France’s leadership will require a shared effort from institutions, clinicians, patient groups and industry. By working together to clarify how innovation is valued and how access pathways can be optimised within realistic budget constraints, France can maintain the strength of its current model while ensuring that it remains a driving force for scientific and medical progress in the years ahead.

How do you see France supporting Alnylam’s future launches, and how are you preparing for the 2026-2027 horizon?

Our ambition is clear. We intend to bring every new therapy to French patients without delay. At the global level, there is no hesitation about future launches in France. The real work lies in demonstrating value within a system that defines innovation through strict methodological criteria. Clinical experts and patient groups often have a broader view, because they see the day-to-day impact of treatment. A move from daily medication to an injection every six months can transform a patient’s life and ease pressure on care pathways. Ensuring these dimensions are recognised remains a central part of our dialogue with the authorities.

France operates under a closely regulated pricing framework led by the Economic Committee for Health Products (CEPS). Prices are public, generally around fifteen percent lower than in many comparable European markets, and often paired with caps, rebates or volume agreements designed to contain expenditure for innovative medicines. Medicines account for roughly thirteen to sixteen percent of national health spending, according to DREES and the national health insurance system, yet the sector has carried a significant share of cost-containment efforts in recent years. If the debate focuses exclusively on price, there is a real risk of slowing patient access to innovation at a time when the health system remains under financial strain post-COVID.

Looking ahead, France’s ability to stay at the forefront of therapeutic innovation will depend on a more coordinated approach. Clinicians, patient organisations, public authorities and industry all need to align on how innovation is defined and how evaluation and reimbursement timelines can be streamlined. The aim is not to change the fundamentals of the French model, but to optimise it so that patients with serious conditions are not left waiting for therapies that could alter the course of their disease.

Which priorities will guide Alnylam France over the next two years as the RNAi landscape expands?

Alnylam’s trajectory in France has changed markedly in a short period of time. We started with a modest, almost start-up presence, yet we now hold a recognised position within the ecosystem after introducing four RNAi therapies in just a few years. These treatments received solid ASMR assessments, which helped them integrate quickly into clinical practice, and despite being a compact team of around thirty-three people, the commitment and agility of our colleagues have been decisive in sustaining this pace.

As we look ahead, our foremost priority is the upcoming indication extension for vutrisiran in transthyretin amyloidosis, specifically its new approval in cardiac amyloidosis, whether hereditary or wild-type. When you work with a highly innovative platform and a relatively small number of marketed products, each new indication carries significant weight, so ensuring that this extension reaches patients as early as possible will be central to our efforts with the authorities.

In parallel, we will continue strengthening our collaboration with clinicians and reference centres. Reducing diagnostic delays and preparing the medical community for the next wave of RNAi innovation remain essential, and these partnerships are key to both objectives. Alongside the launch work, we intend to deepen the research collaborations already active in France, which play an important role in advancing the field. For me, the goal is clear. I want Alnylam’s therapies to reach French patients as quickly as possible, and this focus will guide our work throughout 2026 and 2027.

How do you embed Alnylam’s “Challenge Accepted” mindset within the affiliate and translate it into daily practice?

For us, “Challenge Accepted” is not a slogan but an attitude that has shaped the affiliate since its creation. Introducing an entirely new therapeutic class in France required us to navigate early access pathways, work closely with clinicians, and find practical solutions to ensure patients could receive RNAi therapies without delay. That experience set the tone for how we operate, combining scientific ambition with a strong sense of responsibility toward the people who stand to benefit from these innovations.

Our scale reinforces this mindset. Alnylam France remains a compact organisation, and that reality demands agility. Everyone contributes beyond the boundaries of their formal role, and leadership is

rooted in active involvement rather than hierarchy. In a team of this scale, progress is collective, and each person’s commitment is visible in the work we deliver every day. It creates an environment where shared purpose is not an abstract idea but something you feel in the way the team operates.

The same approach guides how we engage the broader medical community. Introducing RNA interference into routine practice means helping specialists across different fields understand a genuinely new scientific paradigm, and doing so in ways that are practical, credible and tailored to their needs. It requires focus, creativity and sustained partnership with France’s network of reference centres. At its core, the mindset is straightforward. Stay engaged, stay adaptable, and make sure that innovation reaches the patients who stand to benefit from it.

How is Alnylam perceived within the French ecosystem today, and what developments might shape its visibility in the coming years?

Alnylam’s profile in France has grown steadily since 2018, as more clinicians, institutions, and patient associations have engaged with RNA interference and seen its clinical impact. For now, our visibility remains anchored in the rare disease space, which naturally limits broader recognition. As our portfolio extends into more prevalent conditions, notably in cardiometabolic and neurological disorders, the reach of the technology will widen, and the perception of Alnylam will evolve accordingly.

We are still in a formative phase, but progress over recent years has been meaningful. When we meet with institutional stakeholders or peers from other companies, there is a clear sense of interest in the scope of the platform. The science reinforces this attention. We now have well-established hepatic delivery, and our next-generation work moves into the central nervous system with programmes such as ALN-APP in Alzheimer’s disease and cerebral amyloid angiopathy, and ALN-HTT02 in Huntington’s disease. In parallel, zilebesiran, developed with Roche as a twice-yearly subcutaneous treatment for hypertension, illustrates how RNAi could reshape conditions far beyond rare diseases. This breadth naturally attracts interest, and it is positive to see other laboratories investing in the modality. It signals both confidence in the field and the scale of its long-term potential.

What message would you share with an international audience regarding France’s role in innovation, rare diseases, and patient access to care?

France has long been a significant contributor to global science, and it must continue to hold this position. Achieving this requires a shared commitment to valuing innovation in a balanced way and ensuring that institutions, clinicians, patient organisations, and industry work together to define what true therapeutic progress represents. The objective is straightforward. Patients must be able to access safe, effective, and meaningful treatments as early as possible.

Ultimately, everything comes back to them. Behind each assessment process or access debate are individuals living with serious conditions who depend on innovation to alter the course of their disease and improve their quality of life. Ensuring timely access is not just a policy matter. It is a responsibility toward these patients, and it should guide the way we shape the system in the years ahead.

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