Widening the horizons of oligonucleotide drug platforms

Companies that have pioneered platforms based on oligonucleotides targeting RNA and their biopharma partners continue to move beyond rare diseases into broader patient populations with cardiovascular diseases and central nervous system disorders.

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In 1998, Andrew Fire and Craig Mello reported their Nobel prize-winning discovery of the RNA interference (RNAi) pathway for gene regulation. Now, 25 years on, small interfering RNAs (siRNAs) that harness RNAi to silence the expression of selected genes by degrading their messenger RNAs (mRNAs) are a validated therapeutic platform. Together with antisense oligonucleotide (ASO) therapies, the first validated mRNA-targeted platform, siRNA drugs are progressing from their initial testing grounds in rare conditions to common disorders ranging from atherosclerotic cardiovascular disease (ASCVD) to Alzheimer's disease.

Partnerships between large biopharma companies and the companies that have built these platforms over the past few decades continue to have a key role in these advances. With the help of data from DealForma, this article highlights a selection of these deals for cardiovascular diseases and central nervous system (CNS) disorders, and the oligonucleotide therapies underlying them.

Cardiovascular diseases

The first oligonucleotide therapy to be approved for a cardiovascular disease, the ASO Kynamro (mipomersen), was developed through a partnership between Ionis Pharmaceuticals and Genzyme that began in 2008. It received approval from the US Food and Drug Administration (FDA) in 2013 for homozygous familial hypercholesterolemia, a rare disorder characterized by high levels of low-density lipoprotein cholesterol (LDL-C). However, side effects including liver toxicity thought to be linked to the high doses used led to its market withdrawal.

The current generation of oligonucleotide therapies for cardiovascular disease, which harness *N*-acetylgalactosamine (GalNAc) conjugation to enable specific delivery to the liver and thus allow the use of lower doses, are being aimed towards larger patient populations. At the forefront is Leqvio (inclisiran). This siRNA drug inhibits the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme that has a key role in cholesterol homeostasis. Inclisiran, which stemmed from a deal between Alnylam and The Medicines Company, was in late-stage development when Novartis acquired The Medicines Company for $9.7 billion in 2019 (Table 1). In 2021, Novartis saw its investment bear fruit with the FDA approval of Leqvio for lowering LDL-C in patients with ASCVD or heterozygous familial hypercholesterolemia.

PCSK9 is an exemplar of a genetically validated target—gain-of-function mutations cause hypercholesterolemia, while loss-of-function mutations lower LDL-C and reduce the risk of heart disease. Consequently, all sorts of therapeutic modalities have been explored to inhibit its activity (*Nat. Rev. Drug Disc.* **16**, 299–301; 2017). The first two PCSK9-targeted drugs to market were monoclonal antibodies, Regeneron's Praluent (alirocumab) and Amgen's Repatha (evolocumab), which gained FDA approval in 2015.

Sales of these antibody therapies have not been as strong as initially forecast, however, in part owing to their high prices relative to oral drugs used to lower LDL-C, such as the now-generic statins, and the need to inject the antibodies every 2–4 weeks. A hope with inclisiran is that its dosing twice a year as an injection could support wider uptake, while addressing an important real-world issue with daily pills such as statins: treatment adherence even among people who have had heart attacks may often not be as high as needed to maximally reduce the risk of cardiovascular events.

High levels of Lp(a), a lipoprotein that has similarities to LDL-C, independently increase the risk of cardiovascular disease, but its levels are not effectively reduced by statins. For this target, which also has strong genetic validation, there is a head-to-head competition between the ASO and siRNA platforms. In 2020, Novartis launched a phase 3 trial involving more than 8,000 people with established cardiovascular disease to assess whether reducing Lp(a) levels with an ASO called pelacarsen could reduce the risk of cardiovascular events. Enrolment in the trial was completed in 2022 and top-line data are expected in 2025. Novartis also gained pelacarsen through dealmaking, this time with Ionis, paying $150 million to exercise an option to license the ASO in 2019 (Table 1).

Olpasiran, an siRNA candidate that lowers Lp(a) levels, originates from a partnership with a headline value of up to $674 million between Arrowhead Pharmaceuticals and Amgen initiated in 2016 (Table 1). A phase 3 trial of olpasiran that is intended to enroll around 6,000 patients with ASCVD began in 2022, triggering a $25 million payment from Amgen to Arrowhead.

Two further siRNA candidates that lower Lp(a) levels are in phase 2. Enrolment of around 160 patients in a phase 2 trial of Silence Therapeutics' zerlasiran was completed in January, and enrolment in a phase 2 trial of Eli Lilly's lepodisiran involving about 250 patients is also complete. This siRNA candidate originates from a 2018 partnership between Lilly and Dicerna Pharmaceuticals with a headline value of $3.7 billion (Table 1). Dicerna was subsequently acquired by Novo Nordisk for $3.3 billion in a deal announced in 2021.

The latest major deal in the cardiovascular disease area was also around an siRNA, zilebesiran, which acts to reduce blood pressure by inhibiting the production of angiotensinogen (Table 1). This protein is a component of the renin–angiotensin system, which is the target for many widely used anti-hypertensive drugs. In July, Alnylam signed a deal with Roche to co-develop and co-commercialize zilebesiran, through which Alnylam received $310 million

Table 1 | Selected partnerships around oligonucleotide drugs for cardiovascular diseases*

Drug (platform; target)	Company; partner	Indications (development status)	Deal activity
Inclisiran (siRNA; PCSK9)	Alnylam; Novartis	HeFH or ASCVD (approved)	Novartis acquired The Medicines Company for $9.7 billion in 2019, gaining inclisiran, an siRNA drug that was then in late-stage development for lowering LDL-C. The drug was being developed through a partnership established in 2013 between Alnylam and The Medicines Company, with a headline value of $205 million.
Eplontersen (ASO; TTR)	Ionis Pharmaceuticals; AstraZeneca	ATTR-CM (phase 3) and ATTR-PN (submitted for approval)	In 2021, Ionis signed a deal with AstraZeneca to develop and commercialize eplontersen, involving a $200 million upfront payment and up to $3.4 billion in milestones. In July 2023, Ionis expanded the deal by granting exclusive rights to AstraZeneca in Latin America, receiving a further $20 million up front and increasing the total milestones to $3.6 billion.
Pelacarsen (ASO; Apo(a))	Ionis Pharmaceuticals (Akcea Therapeutics); Novartis	Established cardiovascular disease and elevated levels of Lp(a) (phase 3)	In 2019, Novartis paid $150 million to exercise its option to license pelacarsen (then known as TQJ230) under a 2017 agreement with Ionis and its subsidiary Akcea.
Olpasiran (siRNA; Apo(a))	Arrowhead Pharmaceuticals; Amgen	ASCVD and elevated levels of Lp(a) (phase 3)	Arrowhead and Amgen signed a collaboration on two siRNA programs with a headline value of $674 million in 2016. A $25 million milestone payment from Amgen was triggered by the enrolment of the first patient in Amgen's phase 3 trial of olpasiran in 2022.
Lepodisiran (siRNA; Apo(a))	Dicerna Pharmaceuticals; Eli Lilly	Elevated levels of Lp(a) (phase 2)	In 2018, Dicerna and Lilly announced a licensing and research collaboration on siRNAs for cardio-metabolic disease, neurodegeneration and pain with a headline value of more than $3.7 billion, including an upfront payment of $100 million to Dicerna and an equity investment of $100 million in the company. Novo Nordisk acquired Dicerna for $3.3 billion in 2021.
Zilebesiran (siRNA; AGT)	Alnylam; Roche	Hypertension (phase 2)	In July 2023, Alnylam announced a partnership with Roche to co-develop and co-commercialize zilebesiran. Alnylam received $310 million upfront and is eligible to receive milestones that could bring the total deal value to $2.8 billion.

AGT, angiotensinogen; Apo(a); apolipoprotein(a); ASO, antisense oligonucleotide; ASCVD, atherosclerotic cardiovascular disease; ATTR-CM; transthyretin amyloidosis cardiomyopathy; ATTR-PN, transthyretin amyloidosis polyneuropathy; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA; TTR, transthyretin. *Other unpartnered oligonucleotide drugs are in development for the targets listed, such as vutrisiran for ATTR-CM, IONIS-AGT-L_{Rx} and ION904 for AGT and zerlasiran for Lp(a). Unpartnered oligonucleotide drugs are also in development for other cardiovascular disease targets, including apoC-III (olezarsen and plozasiran), angiopoetin-like 3 (zodasiran) and coagulation factor XI (fesomersen).

upfront and is eligible to receive milestones up to a total deal value of $2.8 billion. Two months later, Alnylam announced that a phase 2 study of zilebesiran involving patients with hypertension at high cardiovascular risk met the primary endpoint by resulting in a clinically significant reduction in blood pressure.

Two ASOs that target angiotensinogen, IONIS-AGT-L_{Rx} and ION904, are also in phase 2 development for treatment-resistant hypertension.

Central nervous system disorders

As with cardiovascular diseases, rare conditions have been at the leading edge of progress in treating CNS disorders with oligonucleotide therapies. The first to make it to market, and also the first blockbuster among oligonucleotide therapies overall, is Spinraza (nusinersen). This ASO, which was developed through a partnership between Ionis and Biogen signed in 2012 (Table 2), was approved by the FDA for the treatment of spinal muscular atrophy (SMA) in 2016. The drug acts differently to oligonucleotide therapies that inhibit the function of their targets; it binds to the pre-mRNA for the survival of motor neuron 2 (*SMN2*) gene and modulates splicing to produce a functional form of the SMN protein, which is deficient in people with SMA.

The most recent ASO to reach the market for a CNS disorder, Qalsody (tofersen), stems from a partnership between Biogen and Ionis as well (Table 2). It was granted accelerated approval by the FDA in 2023 for the small subset of people with amyotrophic lateral sclerosis (ALS) who have a mutated form of superoxide dismutase 1 (SOD1) that is targeted by the ASO. Although the drug missed the primary endpoint in a phase 3 trial, which was based on the functional status of patients, it was approved based on its ability to lower blood levels of neurofilament light (NfL), an emerging biomarker of neuronal injury (*Nat. Rev. Drug Disc.* **22**, 431–434; 2023).

Ionis and Biogen also have a partnered ASO in development for most forms of ALS. BIIB105, which targets ataxin 2, modulates the aggregation of a protein called TDP-43 that has a key role in ALS pathogenesis. Drug candidates that affect TDP-43, in this case by inhibiting the kinase PIKFYVE, were also the focus of a deal in September between Takeda and AcuraStem. Takeda agreed to pay up to around $580 million to develop and commercialize AcuraStem's PIKFYVE inhibitors, including the ASO AS-202, which is in preclinical development.

Huntington's disease is another rare neurodegenerative condition for which ASOs have been investigated as therapies. Tominersen, an ASO designed to lower levels of the mutant huntingtin (mHTT) protein that causes Huntington's disease, has been developed through a partnership between Ionis and Roche initiated in 2013 (Table 2). In 2021, a phase 3 trial of the ASO was terminated early after it failed to show evidence of clinical benefit and performed worse than placebo in patients receiving the ASO more frequently. However, Roche has since initiated a phase 2 trial of tominersen in patients with less-severe disease, based on exploratory analyses of the failed trial that suggested such patients may be more likely to benefit from ASO therapy. Wave Life Sciences and its partner Takeda also have an ASO that affects mHTT in a phase 1/2 trial (Table 2), and Roche has invested further in the ASO platform recently, signing a deal in September involving an upfront payment of $60 million to Ionis to advance two preclinical programs: one also for Huntington's disease and one for Alzheimer's disease.

Recent data from an early-stage clinical trial of another ASO for Alzheimer's disease have provided a preliminary indication that this much more common disease—and one for which there have been many costly clinical trial failures over the past two decades—might be targetable with oligonucleotide therapies. In April, Biogen published a paper on a phase 1b trial showing that the ASO BIIB080 resulted in reductions in CNS levels of the protein tau, which forms aggregates that are one of the hallmarks of Alzheimer's disease (*Nat. Med.* **29**, 1437–1447; 2023). The ASO, developed in partnership with Ionis (Table 2), is now in a phase 2 trial.

Encouraging initial phase 1 findings in people with Alzheimer's disease have also recently been reported for the first siRNA candidate to enter the clinic for a CNS disorder, ALN-APP, which is being developed through a partnership established between Alnylam and Regeneron in 2019 (Table 2). The siRNA targets amyloid precursor protein (APP), which is processed into the

Table 2 | Selected partnerships around oligonucleotide drugs for central nervous system disorders*

Drug (platform; target)	Company; partner	Indication (development status)	Deal activity
Nusinersen (ASO, SMN2)	Ionis Pharmaceuticals; Biogen	Spinal muscular atrophy (approved)	Nusinersen was developed through a partnership established in 2012 between Ionis (then called Isis Pharmaceuticals) and Biogen with a headline value of $299 million.
Tofersen (ASO, SOD1)	Ionis Pharmaceuticals; Biogen	ALS associated with a *SOD1* mutation (approved)	In 2018, Biogen paid Ionis $35 million to exercise its option to license tofersen (then called BIIB067), which was developed through a partnership established in 2013.
Tominersen (ASO, HTT)	Ionis Pharmaceuticals; Roche	Huntington's disease (phase 2)	Roche paid Ionis $45 million in 2018 to exercise its option to license tominersen (then called IONIS-HTT_{Rx}), which has been developed through a 2013 alliance on Huntington's disease with a headline value of $392 million.
BIIB080 (ASO, tau)	Ionis Pharmaceuticals; Biogen	Alzheimer's disease (phase 2)	In 2019, Biogen exercised its option to BIIB080, then known as IONIS-$MAPT_{Rx}$. Ionis received $45 million upfront and is eligible to earn up to $155 million in milestones.
BIIB105 (ASO, ATXN2)	Ionis Pharmaceuticals; Biogen	ALS (phase 2)	BIIB105, also known as ION541, has been developed through a partnership established in 2013.
WVE-003 (ASO, mHTT)	Wave Life Sciences; Takeda	Huntington's disease (phase 1/2)	In 2018, Takeda paid Wave $110 million upfront, made a $60 million equity investment in Wave, and agreed to spend at least $60 million on the development of multiple candidates for CNS disorders, including WVE-003.
BIIB094 (ASO, LRRK2)	Ionis Pharmaceuticals; Biogen	Parkinson's disease (phase 1/2)	In 2022, Ionis received a $10 million milestone payment linked to the advancement of a phase 1/2 study of BIIB094 (also known as ION859), which has been developed through a partnership established in 2013.
BIIB101 (ASO, SNCA)	Ionis Pharmaceuticals; Biogen	Multiple system atrophy (phase 1/2)	BIIB101 (also known as ION464) has been developed through a partnership established in 2013.
BIIB121 (ASO, UBE3A)	Ionis Pharmaceuticals; Biogen	Angelman syndrome (phase 1/2)	BIIB121 (also known as ION582) has been developed through a partnership established in 2012.
BIIB115 (ASO, SMN2)	Ionis Pharmaceuticals; Biogen	Spinal muscular atrophy (phase 1)	In 2021, Biogen paid $60 million to Ionis to exercise its option to develop and commercialize BIIB115 (also known as ION306), which has been developed through a deal signed in 2017.
ALN-APP (siRNA; APP)	Alnylam; Regeneron	Alzheimer's disease and CAA (phase 1)	ALN-APP is being developed through a collaboration between Alnylam and Regeneron on CNS and ocular diseases announced in 2019. Regeneron agreed to pay $400 million in cash and make a $400 million equity investment in Alnylam, and Alnylam is eligible for up to $200 million in milestones.

ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; ASO, antisense oligonucleotide; ATXN2, ataxin 2; CAA, cerebral amyloid angiopathy; CNS, central nervous system; HTT, Huntingtin protein; LRRK2, leucine-rich repeat kinase 2, siRNA, small interfering RNA; SMN2, survival motor neuron protein 2; SNCA, α-synuclein; SOD1, superoxide dismutase 1; TTR, transthyretin; UBE3A, ubiquitin protein ligase E3A. *Unpartnered oligonucleotide drugs are also in development for other CNS targets, including FUS (ulefnersen), glial fibrillary acidic protein (zilganersen), UBE3A (GTX-102) and SCN1A (STK-001).

amyloid-β peptide that aggregates into the hallmark plaques in Alzheimer's disease. Alnylam presented results at the Alzheimer's Association International Conference in July showing that ALN-APP, which is the first clinical candidate to use its 2′-*O*-hexadecyl (C16)–siRNA conjugate platform to promote CNS delivery (*Nat. Biotechnol.* **40**, 1500–1508; 2022), resulted in sustained reductions in CNS levels of APP over six months with a single dose.

Platform partnering

While the path to approval for candidates such as BIIB080 and ALN-APP from this point is fraught with potential pitfalls, the hope is that these oligonucleotide therapies could finally unlock disease-linked molecules such as tau and amyloid-β that have long held biological appeal, but that have proven very difficult to target effectively.

The histories of oligonucleotide platforms from their creation to tackling such targets hold lessons for aspiring therapeutic-platform developers, including insights on the role of partnerships. In the first few years after the foundation of multiple biotech companies to exploit the RNAi pathway in the early 2000s, there was a surge of investment into the field from large pharma companies, including a partnership with a potential value of up to $650 million between Alnylam and Novartis in 2005 and Merck & Co.'s $1.1 billion acquisition of Sirna Therapeutics in 2006. However, as John Maraganore, who became founding CEO of Alnylam in 2002, highlighted in an article last year (*Nat. Biotechnol.* **40**, 641–650; 2022), this investment fell away from 2010 onwards because their pharma partners at the time were having greater challenges with drug delivery than anticipated—in part because they were trying to fit siRNA drugs into their existing therapeutic areas such as oncology, rather than pursuing opportunities that were best-suited to the capabilities of the platform at the time, such as diseases with targets in the liver.

Ultimately, Alnylam brought the first siRNA drug to market on its own in 2018—Onpattro (patisiran) for the treatment of transthyretin amyloidosis polyneuropathy (ATTR-PN), a rare condition for which the characteristics of siRNA technology are well matched, and one that continues to be a focus for next-generation siRNA and ASO therapies (Table 1). While progressing patisiran alone, Alnylam continued to sign deals such as the one in 2013 with The Medicines Company on inclisiran. This drug could now be at the forefront of an era in which oligonucleotide therapies also establish their place as a major modality for common diseases.

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