Global Oligonucleotide Drug Development Status and Trends Postprint

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Abstract

Objective: To analyze the current development status and future trends of oligonucleotide drugs from a product development perspective. Methods: Data from Clarivate Analytics'Cortellis database were retrieved, and the search results were analyzed using quantitative and comparative analysis methods. Results: To date, 7 oligonucleotide drugs have been marketed, 4 are in pre-registration, and 16 are in Phase III clinical trials, indicating a rapid growth trend for oligonucleotide drugs in the future market. Furthermore, commercial transactions for oligonucleotide drugs are also increasing, with over 10 transactions to date including drug development and commercialization licensing, patent asset sales, and early-stage drug R&D collaborations, among which drug development and commercialization licensing is the primary transaction model. Conclusion: Although the oligonucleotide drug market is still in its infancy, with continuous technological development and improvement in the future, more oligonucleotide drugs are expected to be marketed, providing new opportunities for the treatment of cancer and other diseases.

Full Text

Preamble

Global Development Status and Trends of Oligonucleotide Therapeutics

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Abstract

Objective: To analyze the development status and future trends of oligonucleotide therapeutics from a product development perspective. **Methods:** Data

from Clarivate Analytics' Cortellis database were retrieved and analyzed using quantitative and comparative analysis methods. **Results:** Currently, 7 oligonucleotide therapeutics have been launched, 4 are in pre-registration, and 16 are in Phase III clinical trials, indicating a rapid growth trend in the future market. Additionally, commercial transactions involving oligonucleotide therapeutics are increasing, with over 10 deals recorded to date, including drug development and commercial licensing, patent asset sales, and early-stage R&D collaborations, among which drug development and commercial licensing represents the primary transaction model. **Conclusion:** Although the oligonucleotide therapeutics market is still in its infancy, continuous technological development and improvement will likely bring more oligonucleotide drugs to market, providing new opportunities for treating cancer and other diseases.

Keywords: Oligonucleotide therapeutics; Market competition; Clinical R&D

Oligonucleotides are short-chain nucleotides of approximately 20 bases, including nucleotides within DNA or RNA [1]. They can readily bind to their complementary strands and are commonly used as probes to determine DNA or RNA structures. Research into their application as drug candidates began approximately 30 years ago, encompassing antisense oligonucleotides, triplex DNA, CpG oligonucleotides, aptamers, decoys, ribozymes, siRNA, microRNA, and others [2]. Oligonucleotides can inhibit or replace the function of certain genes, thus possessing drug development value, and some endogenous oligonucleotides (such as microRNA) are significant for disease diagnosis, treatment, and prognosis evaluation. Currently, the pharmaceutical industry is conducting numerous clinical trials on antisense oligonucleotides, siRNA, and aptamers. Therefore, this paper focuses on oligonucleotide therapeutics, examining their development and market status to provide references for China' s related industries.

1.1 Data Sources

Data were retrieved from Clarivate Analytics'Cortellis database (formerly Thomson Reuters Pharma) on December 7, 2017. Drug development and drug transactions were searched through the "Drugs" and "Deals" portals in advanced search, respectively. Both searches utilized the "Biotechnology concept"category under "Technologies," selecting "Nucleic acid technology" and then "Nucleotide technology," with "Oligonucleotide" identified as the search target within the nucleotide substructure.

1.2 Analysis Methods

The study employed quantitative analysis and comparative analysis. Quantitative analysis involved statistical examination of numerical characteristics, relationships, and changes to provide a foundation for comparative analysis. Comparative analysis identified differences between actual numbers and baseline figures to understand the current status and trends of the research subjects.

2.1 Overall R&D Status

According to Cortellis data, 1,590 oligonucleotide therapeutics have been recorded globally. Excluding drugs that are suspended, terminated, or have no R&D reports, 731 drugs are currently in active development. The vast majority of products are in discovery and clinical stages, with discovery-stage products accounting for 36.1% of the total and clinical-stage products representing 9.2%, demonstrating increasing R&D activity in oligonucleotide therapeutics.

[Figure 1: see original paper]

2.2 Important Product R&D Progress

Currently, 27 products are in Phase III clinical trials, registration, or launched stages, all of which are either already on the market or highly likely to benefit patients. These include 7 launched products (Table 1), 4 in pre-registration (Table 2), and 16 in Phase III clinical trials (Table 3). Analysis of launch countries and regions reveals that developed nations are priority markets for oligonucleotide therapeutics, attributable to their advanced research technologies, well-established drug review processes, and regulatory systems. However, developing countries such as India, Brazil, and Israel also have oligonucleotide therapeutics entering registration and Phase III clinical stages.

2.2.1 Launched Products

(1) Mipomersen sodium/Kynamro
Developed jointly by Ionis Pharmaceuticals and Kastle Therapeutics, Mipomersen Sodium (trade name: Kynamro) was approved by the U.S. Food and Drug Administration (FDA) on January 29, 2013, for patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to lipid-lowering medications and diet to reduce low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), total cholesterol (TC), and non-high-density lipoprotein cholesterol (non-HDL-C) [3]. Mipomersen Sodium is an antisense oligonucleotide targeting human apo B-100 messenger RNA; apo B-100 is the primary apolipoprotein of LDL and its metabolic precursor, very low-density lipoprotein. Administered as a weekly injection in combination with lipid-lowering drugs and diet, it blocks secretion of fatty microdroplets. A clinical study involving 51 HoFH patients evaluated its efficacy and safety, showing that subjects receiving Mipomersen Sodium experienced an average 25% reduction in LDL-C during the first 26 weeks of treatment. The most common adverse reactions included injection site reactions, flu-like symptoms, nausea, headache, and elevated liver enzyme levels.

(2) Nusinersen/Spinraza
Developed by Ionis Pharmaceuticals and Biogen, Nusinersen (trade name: Spinraza) received FDA approval on December 23, 2016, and EMA approval on June 1, 2017, for the treatment of spinal muscular atrophy (SMA) in children and adults, marking the first FDA-approved drug for this disease. Nusinersen is an

antisense oligonucleotide that treats SMA caused by deficiency of survival motor neuron (SMN) protein due to chromosome 5q mutations. In vitro analysis and studies in SMA transgenic animal models demonstrated that Nusinersen increases exon 7 inclusion in SMN2 mRNA transcripts and produces full-length SMN protein containing exon 7 [4]. As an injectable formulation administered directly into the cerebrospinal fluid surrounding the spinal cord, it is suitable for all types of SMA patients. Clinical trials validated its efficacy, showing that 40% of patients in the treatment group exhibited improved motor function, while no patients in the control group showed such improvement.

(3) Eteplirsen/Exondys 51

Developed by Sarepta Therapeutics, Eteplirsen (trade name: Exondys 51) received accelerated FDA approval on September 19, 2016, for Duchenne muscular dystrophy (DMD) patients amenable to exon 51 skipping. Eteplirsen employs a novel phosphorodiamidate morpholino oligonucleotide and exon-skipping technology to restore the mRNA reading frame and partially correct genetic defects. As an antisense RNA, it binds to dystrophin pre-messenger RNA exon 51, removing exon 51 in patients with gene mutations that permit exon skipping during messenger RNA processing. Approximately 13% of DMD patients may be eligible for this exon 51-targeted therapeutic approach [5].

(4) Defibrotide Sodium/Defitelio

Developed by Gentium, Defibrotide Sodium (trade name: Defitelio) received EU approval on October 22, 2013, and FDA approval on March 30, 2016, for the treatment of severe hepatic veno-occlusive disease (HVOD) in adults and children following hematopoietic stem cell transplantation (typically complicated by renal and pulmonary dysfunction), representing the first FDA-approved drug for severe HVOD [6]. Defibrotide Sodium is a single-stranded oligonucleotide mixture with antithrombotic and profibrinolytic effects. Originally developed by Gentium, it was acquired by Jazz Pharma in 2013 through its $1 billion acquisition of the Italian pharmaceutical company. A clinical trial involving 528 patients demonstrated that HVOD patients treated with Defibrotide Sodium had survival rates of 38-45% at 100 days post-hematopoietic stem cell transplantation (HSCT), compared to only 21-31% for patients receiving supportive care alone.

(5) Rintatolimod/Rintamod

Developed by Hemispherx Biopharma, Rintatolimod (trade name: Ampligen) received New Drug Application (NDA) approval from Argentina' s Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica (ANMAT) on March 6, 2017, for the treatment of myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) (ME/CFS) [7]. Rintatolimod is an RNA oligonucleotide and the first globally approved drug for this indication. Marketed by Hemispherx' s Latin American commercial partner GP Pharm, both companies are working to expand rintatolimod' s approval to other countries, with a focus on Latin America.

(6) Pegaptanib Sodium/Macugen

Developed by NeXstar, Pegaptanib Sodium (trade name: Macugen) received FDA approval in December 2004 as the only anti-VEGF aptamer for age-related macular degeneration (AMD). As a chemically synthesized oligonucleotide sequence with high affinity for vascular endothelial growth factor (VEGF), it blocks blood vessel growth and inhibits neovascularization, demonstrating therapeutic effects on choroidal neovascularization (CNV) of any size and composition. Its sodium salt is used to treat wet AMD [8]. Originally developed by NeXstar and transferred to EyeTech in 2000, Pfizer managed the U.S. market, achieving $185 million in sales in 2005. However, following the launch of antibody drugs Lucentis, Avastin, and Eylea, sales dropped to $5 million in 2006 and $1.2 million in 2008.

(7) Fomivirsen/Vitravene
Developed jointly by Ionis Pharmaceuticals and Novartis, Fomivirsen (trade name: Vitravene) received FDA approval in 1998 and EU EMA approval in 1999. As the first FDA-approved antisense oligonucleotide drug, it consists of 21 phosphorothioate deoxynucleotides with the sequence 5' -GCGTTTGCTCTTCTTCTTGCG-3' , primarily used to treat cytomegalovirus (CMV) retinitis in AIDS patients. It exerts specific and potent antiviral effects through antisense inhibition of human CMV mRNA, offering long-lasting efficacy, infrequent dosing, and mild adverse reactions [9]. Initially, market demand for anti-CMV drugs was urgent, but cases declined dramatically following the development of highly active antiretroviral therapy, leading to market withdrawal in Europe in 2002 and in the U.S. in 2006.

2.2.2 Pre-registration

(1) Patisiran
In September 2017, Alnylam Pharmaceuticals and Sanofi' s Genzyme announced excellent results from Phase 3 clinical trials of their RNAi drug patisiran for treating polyneuropathy hereditary ATTR amyloidosis [10]. Patisiran utilizes the body' s natural mechanisms to reduce TTR protein levels that cause TTR amyloidosis by targeting and silencing specific messenger RNA to block TTR protein production, helping clear TTR amyloid deposits in peripheral tissues and restore their function. Alnylam submitted its first NDA in November 2017, followed by a marketing authorization application. Beginning in the first half of 2018, Sanofi Genzyme prepared regulatory filings for patisiran in Japan, Brazil, and other countries. Upon regulatory approval, Alnylam will commercialize patisiran in the U.S., Canada, and Western Europe, while Sanofi Genzyme will commercialize it in other regions.

(2) Volanesorsen
In December 2016, Akcea Therapeutics and Ionis Pharmaceuticals completed Phase III clinical trials for Volanesorsen, demonstrating significant reductions in patients' triglyceride levels [11]. Volanesorsen is designed to treat two metabolic diseases: familial chylomicronemia syndrome (FCS) and familial partial lipodystrophy (FPL). In August 2017, Akcea Therapeutics submitted an NDA to the

U.S. FDA for volanesorsen to treat familial chylomicronemia syndrome (FCS), with expected launch in 2018.

(3) Inotersen
At the 2017 Peripheral Nerve Society annual meeting, Ionis Pharmaceuticals presented updated Phase 3 clinical trial data for Inotersen, a drug candidate for familial amyloid polyneuropathy (FAP) [12]. Inotersen is an antisense nucleotide drug specifically targeting transthyretin (TTR) amyloidosis that can inhibit production of all TTR proteins (both mutant and wild-type). The drug has demonstrated strong and durable efficacy in inhibiting TTR protein expression in clinical trials across various diseases caused by TTR protein amyloidosis. For FAP indications, Inotersen has received orphan drug and fast-track designations from the U.S. FDA and orphan drug designation from the European EMA. In November 2017, Ionis Pharmaceuticals submitted an NDA to the U.S. FDA for Inotersen to treat FAP, with expected launch in 2018.

(4) Alicaforsen
Alicaforsen is an antisense oligonucleotide against intercellular adhesion molecule 1 (ICAM-1) for the treatment of chronic enteritis and pouchitis [13]. In May 2017, Atlantic Healthcare submitted an NDA to the U.S. FDA for Alicaforsen to treat diverticulitis.

2.2.3 Phase III Clinical Trials

In addition to launched products and those in NDA stages, multiple products have entered Phase III clinical trials. For example, the oligonucleotide therapeutic QPI-1007 is being developed for non-arteritic anterior ischemic optic neuropathy (NAION) and has potential for glaucoma treatment. Suzhou Ribo Life Science and its strategic partner Quark Pharmaceuticals have received CFDA approval in China for an international multicenter clinical trial of QPI-1007. This approval covers an international multicenter Phase II/III pivotal study for NAION. QPI-1007 has previously received orphan drug designation from the U.S. FDA and represents the first oligonucleotide therapeutic approved for clinical trials in China. Development and market rights for this drug in China and the Asian region (excluding certain specific countries) are held by Kunshan RiboQuark Pharmaceutical Technology, registered at the Kunshan Small Nucleic Acid Base.

Other products in Phase III include QPI-1002, Cobitolimod/Kappaproct, and Inclisiran/ALN-PCSsc (Table 3). Inclisiran is a small interfering RNA (siRNA) drug developed by Alnylam Pharmaceuticals, featuring polysaccharide group modification and hepatocyte targeting. Belagenpumatucel-L, developed by NovaRx, is an allogeneic vaccine genetically modified to express an antisense transgene plasmid containing the immunosuppressive factor transforming growth factor-$ 2(TGF- 2), blockingTGF- $2' s immunosuppressive effects and preventing tumor cell immune evasion. Tivanisiran, developed by Sylentis, is a chemically synthesized small interfering RNA (siRNA) inhibitor of the capsaicin

receptor (TRPV1) for ocular pain treatment. Aganirsen is a DNA translation oligonucleotide that inhibits insulin receptor substrate 1 (IRS-1) and is being investigated for treating ocular neovascularization.

2.3 Product Transaction Status

The oligonucleotide therapeutics R&D field currently features three main transaction types: drug development and commercial licensing, patent asset sales, and early-stage drug R&D collaborations. Among these, drug development and commercial licensing represents the primary transaction form, accounting for 50% of all transactions (Table 4). Key transactions include:

(1) **Ionis and Novartis $1.6 Billion Agreement for Two Lipid-Lowering RNA Drugs**
On January 5, 2017, Novartis signed a $1.6 billion collaboration agreement with Ionis' subsidiary Akcea, including $225 million in near-term payments, to jointly develop lipid-lowering RNA drugs AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx. Akcea would receive $75 million upfront and $100 million in stock purchases. However, on February 16, 2017, Ionis announced that it and its subsidiary Akcea would terminate the exclusive collaboration agreement with Novartis for global development and commercialization of AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx.

(2) **Alnylam and Vir $1 Billion Agreement for Novel RNAi Therapies**
On October 18, 2017, Alnylam, a leader in RNAi therapy development, signed a $1 billion agreement with California-based Vir Biotechnology to develop and market the RNAi therapy ALN-HBV-02 for hepatitis B virus infection treatment. The partnership will advance Alnylam' s hepatitis B virus program while collaborating on up to four additional RNAi therapies for other infectious diseases.

(3) **Sosei Acquires 25.6% Stake in MiNA for saRNA Technology**
On May 2, 2017, Japanese pharmaceutical company Sosei acquired a 25.6% stake in MiNA Therapeutics for $45 million cash, obtaining an exclusive option on the company. MiNA is currently conducting Phase I/IIa trials of small activating RNA (saRNA) technology in liver cancer. If successful, Sosei will complete a transaction totaling $534 million, comprising $180 million cash plus $309 million in milestones.

(4) **Boehringer Ingelheim and MiNA $350 Million Agreement for NASH RNA Therapy**
On November 8, 2017, Boehringer Ingelheim and MiNA Therapeutics signed a collaboration and licensing agreement worth $355 million to develop RNA therapies for liver fibrosis and non-alcoholic steatohepatitis based on MiNA' s saRNA therapy platform.

(5) **IONS and Dynacure $210 Million Agreement for Antisense Drug**

Dyn101
On November 9, 2017, Dynacure and IONS signed a $210 million agreement to develop the antisense-targeted drug IONSDNM2-2.5Rx (Dyn101) for myopathy treatment. IONS received $5 million in license fees in Dynacure equity, with Dynacure now assuming all development and commercialization responsibilities.

(6) **Dicerna and Boehringer Ingelheim $200 Million Agreement for Chronic Liver Disease RNAi Therapy**
On November 27, 2017, Dicerna Pharmaceuticals and Boehringer Ingelheim established a research collaboration and licensing agreement to develop novel RNAi therapies for chronic liver disease, initially focusing on non-alcoholic steatohepatitis (NASH). Under the agreement, Dicerna will receive up to $201 million in upfront, development, and commercial milestone payments, plus eligibility for double-digit royalties on global net sales.

(7) **iPharma Purchases Chinese Patent Rights for Lefitolimod Immunotherapy for $123 Million**
On August 25, 2017, iPharma, a joint venture between incubator I-Bridge Capital and Israeli biopharmaceutical company BioLineRx, signed an agreement with German biotech company Mologen to purchase Chinese patent rights for Mologen' s lead product lefitolimod immunotherapy, with the transaction valued at up to $123 million including royalties. The drug is currently in Phase II clinical trials for colorectal cancer and Phase III for lung cancer.

(8) **Alexion Acquires Arbutus LNP Drug Delivery Technology for $825 Million**
On March 15, 2017, Alexion purchased Arbutus' LNP drug delivery and formulation technology for $825 million to develop single messenger RNA candidates for rare diseases. Under the agreement, Alexion will pay $7.5 million upfront and up to $75 million in development, regulatory, and commercial milestones, plus single-digit royalties.

(9) **Sarepta Pays BioMarin $60 Million for DMD Patent Exclusive License**
On July 17, 2017, Sarepta paid BioMarin $60 million for exclusive patent licensing rights to Duchenne muscular dystrophy products EXONDYS-51 and all exon-skipping products (casimersen, golodirsen).

(10) **AstraZeneca Collaborates with Ethris on Novel RNA Therapy**
On August 21, 2017, AstraZeneca signed a $29.39 million agreement with German company Ethris to co-develop new stable, non-immunogenic modified RNA therapies for respiratory diseases. Ethris will apply its SNIM RNA technology to develop drugs for asthma, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis.

3. Summary and Outlook

Recent advances in oligonucleotide therapeutics R&D have demonstrated tremendous potential in treating previously intractable diseases such as genetic disorders and cancer. However, therapeutic pathways for oligonucleotide drugs remain immature, with many challenges to overcome. For siRNA drugs, primary obstacles include interferon responses in vivo, instability, targeting and off-target effects, delivery systems, administration methods, and safety concerns. Consequently, most small RNA gene drug research remains in early development stages, specifically preclinical research.

After more than two decades of research efforts, the FDA approved two oligonucleotide therapeutics—Eteplirsen and Nusinersen—in 2016, suggesting more oligonucleotide drugs will likely reach the market in the future. With continuous technological development and improvement, long-term stable support from national policies and funding, and ongoing researcher efforts, oligonucleotide therapeutics represented by antisense nucleic acids and siRNA will undoubtedly provide new opportunities for treating cancer and other diseases, creating a new wave in the pharmaceutical industry and becoming an indispensable force in the third-generation pharmaceutical revolution oriented toward gene expression regulation.

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Note: Figure translations are in progress. See original paper for figures.