SECTORAL
ASSET MANAGEMENT

NEWSLETTER

JULY 2014

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HEALTHCARE MARKET REVIEW AND OUTLOOK

Healthcare stocks tracked broadly in line with global markets during the second quarter, following their clear outperformance during Q1. Reporting an increase of 4.7% during the quarter, the MSCI World Healthcare Index now stands at +10.8% for 2014. M&A stands out as the main driver of performance and excitement in the healthcare sector.

Tax considerations have prompted many of the announced, rumored, or otherwise attempted (sometimes failed) deals. In an effort to put offshore cash reserves to use and to lower their overall tax rates, several US based corporations have been targeting non-US companies. By itself, tax optimization would seem to be a pathetic admission of lack of vision, if not strategic failure. Fortunately, and rather reassuringly, Pfizer was sent packing after its attempted USD100bn bid for AstraZeneca. Other deals, however, have more merit, such as Medtronic's USD46bn acquisition of Covidien. In this case, the purchase creates a global leader with complementary product lines.

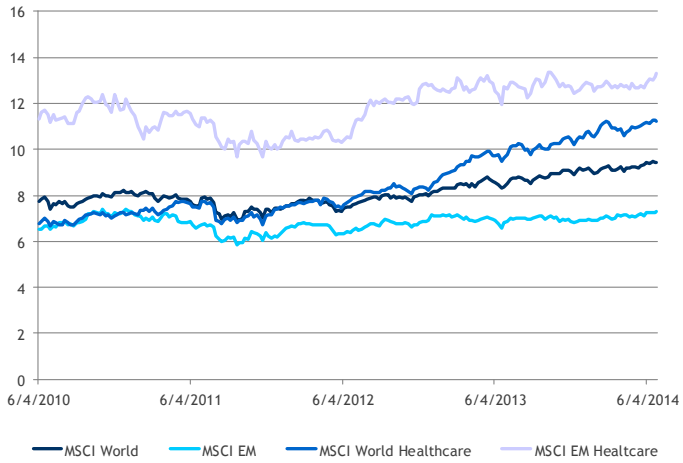
Overall, the main area of acquisition was specialty pharma. The rationales ranged from geographic expansion (eg, Abbott's acquisition of Chilean drugmaker CFR) to business/technology complementarity (eg Hikma's purchase of US-based injectables player Bedford Labs from Boehringer Ingelheim or Mallinckrodt's addition of Questcor for USD5.6bn). Potential restructuring/cost synergies prompted other deals, including Sun Pharma's takeover of Ranbaxy and Valeant's attempt to buy Allergan. The latter has sparked a debate about the role of specialty pharmaceutical companies. Should these concerns solely serve as marketing machines

INDEX	CLOSE 6/30/2014	RETURN					ANNUALIZED VOLATILITY	
		1 MONTH	3 MONTH	6 MONTH	9 MONTH	12 MONTH	3 MONTH	6 MONTH
MSCI World Index (all country)	192.2	1.9%	5.0%	6.2%	13.9%	22.9%	7%	6%
MSC World Index	4598.7	1.8%	4.9%	6.2%	14.7%	24.0%	8%	6%
MSCI World Healthcare Index	237.8	2.3%	4.7%	10.8%	20.7%	28.7%	10%	9%
MSCI World Pharma	197.5	2.2%	4.5%	11.8%	21.2%	27.5%	10%	9%
MSCI World Biotech	1051.0	3.0%	7.8%	8.4%	18.5%	41.1%	24%	21%
MSCI World Equip and Suppl	290.1	3.7%	5.7%	10.6%	19.4%	22.5%	10%	9%
MSCI World Healthcare Providers	349.1	0.9%	2.4%	8.6%	20.7%	26.7%	10%	10%
MSCI Emerging Market Healthcare	510.4	5.2%	8.1%	9.8%	14.8%	17.4%	10%	10%

with slashed R&D budgets (the Valeant model), or should they pursue the traditional model and continue to invest a sizeable, and potentially excessive, portion of their revenue in R&D? Finally, other deals, involving biotech companies as well, were straightforward product acquisitions, among them the USD3.85bn Merck bid for Idenix and Forest Labs' more modest USD1.1bn acquisition of Furiex. Actual M&A was complemented by more or less well-founded rumors surrounding NPS Pharma (a potential acquisition by Shire) and Shire itself (by AbbVie). Corporate restructurings and asset swaps also helped drive prices higher. The most noteworthy deals clearly were the Novartis/Glaxo transactions, which included Novartis' acquisition of Glaxo's oncology assets, the sale of Novartis' vaccine business to Glaxo, and the formation of a JV around their mutual OTC businesses. In addition, Novartis divested its animal health business to Lilly.

Emerging-market healthcare stocks performed strongly. With a quarterly increase of 8.1%, the MSCI Emerging Markets Healthcare Index now stands at +9.8% for 2014, within 100bp of the MSCI World Healthcare Index. These stocks also outperformed their reference markets (8.1% vs 6.6%). Over the last 12 months, however, the gap between emerging-markets healthcare stocks and their global counterparts has remained substantial, more than 1100bps (+17.4% vs +28.7%). Thus, the valuation spread we highlighted in last newsletter continues at its recent historical low; this suggests the opportunity for mid- to long-term-oriented investors is still intact, despite the recent outperformance. Indeed, on an EV/EBITDA basis, emerging-markets healthcare stocks are valued at 13.3x (for the next twelve months). While this valuation is a premium compared with the 11.2x for their developed-markets counterparts, it is justified, given the higher expected growth (14% vs 8%, per Bloomberg data) for these stocks.

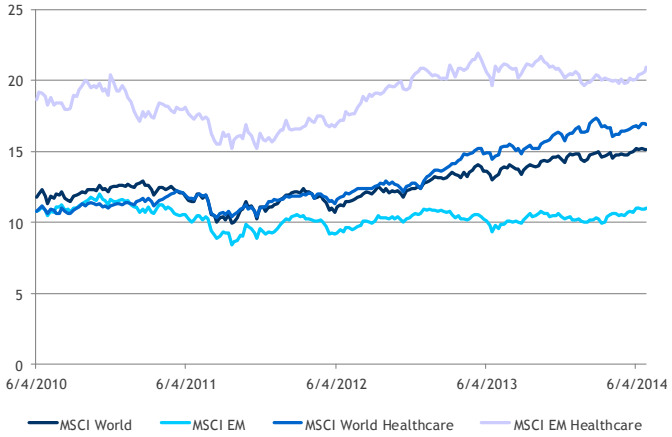
Biotech was once again the healthcare sector's star, as the MSCI World Biotech Index rose 7.8% over the quarter. After the late March-early April sell-off, biotech stocks snapped back and regained virtually all



Forward 12m EV/EBITDA Valuation. Source: Bloomberg.

of the ground lost since their April bottom to return to the highs seen earlier in the year. Strong clinical results triggered much of the recent rally. Some of the more significant news was the positive Phase III data for Vertex's combination lumacaftor/Kalydeco in F508del cystic fibrosis, the success of Actelion's selexipag in pulmonary arterial hypertension, and Synageva's positive Phase III data for sebelipase alpha in patients with lysosomal acid lipase deficiency. In addition, a broad array of positive Phase I/II data was reported, including rolapitant in chemotherapy-induced nausea and vomiting (Tesaro), brodalumab in psoriasis (Amgen), lentiviral gene-therapy vectors for beta-thalassemia (Bluebird Bio), andexanet alpha for the reversal of enoxaparin anticoagulation activity (Portola), selexinor in multiple myeloma (Karyopharm), and positive early data from Agios in various forms of blood cancer. In contrast, Biogen-IDEC and Isis issued a mixed update on SMNRx for spinal muscular atrophy, while Cytokinetics' Phase IIb study of lead-product tirasemtiv in ALS failed, as did Endocyte's Phase III trial of vintafolide for ovarian cancer.

On the regulatory front, much of the positive news was expected, but some surprises helped fuel the biotech rebound. The most noteworthy development was the European CHMP recommendation for PTC Therapeutic's ataluren for nonsense mutation Duchenne muscular dystrophy (DMD). Other



Forward 12m PE Valuation. Source: Bloomberg.

announcements included the FDA guidance allowing Sarepta and Prosensa to file for accelerated approval of their drugs for DMD, as well as the breakthrough designation received by Insmed's Arikayce for nontuberculous mycobacterial infections. The interest in biotech was also mirrored in the continued flow of IPOs. Despite a lull in April, the IPO window remained open, as 15 more deals were completed in the second quarter. Combined with the 25 IPOs recorded during Q1, the year-to-date total to new offerings stands at 40 (vs 59 for the whole of 2013).

The multiple expansion witnessed in the last two to three years, coupled with the ongoing M&A

GROWTH P.A. 2013-2016E					
	SALES	EPS	PE14E	EV/SALES14E	COGS
Pharmaceuticals	2-4%	4-6%	17x	3.9x	15-20%
Generics	10-15%	10-15%	18x	2.6x	25-55%
Biotechs	15-20%	20-25%	24x	8.6x	10-20%
Medtechs	10-15%	15-20%	22x	3.5x	20-40%

Based on Sectoral estimates / median numbers

speculation and flurry of IPOs, are reasons for caution and selectivity. Indeed, healthcare is trading at 20% and 12% premiums relative to global markets, based on the EV/EBITDA multiple and PEs, respectively. Global valuation itself is close to 10x on EV/EBITDA, a high level when viewed from a historical perspective. To be sure, some of this multiple expansion is justified by the recent drug approvals and pipeline progress showcased by both pharmaceutical and biotech companies. That being said, we are cautious on specialty pharmaceuticals and emphasize stock picking among biotech companies. We do have less reservation with managed-care groups, which have benefited from better-than-expected enrollment numbers under the Affordable Care Act. Finally, we see real value in emerging-markets healthcare stocks, from a mid- to long-term perspective, despite the short-term uncertainties surrounding these markets.

Michael Sjöström, CFA
Chief Investment Officer

NUCLEIC ACID THERAPEUTICS

Advances in genomics and the understanding of cellular processes regulating gene expression has led to the development of several new classes of drugs based on nucleic acids. These include drugs based on RNA interference and antisense, as well as an entirely new platform that uses messenger RNA to direct the production of proteins inside a patient's own cells. The mechanisms of nucleic-acid therapeutics include up- and down-regulation of genes and the modulation of RNA processing. All hold significant promise for patients and healthcare investors alike.

It took over 20 years from the time monoclonal antibodies (mAbs) were first developed in 1975 until their therapeutic potential was convincingly demonstrated. Small biotechnology companies focusing on mAbs were formed with much fanfare, only to experience serious clinical setbacks before technical advances enabled the development of compounds with compelling efficacy and safety across a wide range of indications. Today, mAbs are an enormously successful therapeutic modality, generating tens of billions of dollars in sales across many disease conditions. Among them is the world's top selling drug, AbbVie's Humira, which posted 2013 sales of USD10.7bn.

This pattern may now be repeating itself in the different classes of nucleic-acid-based therapeutics.

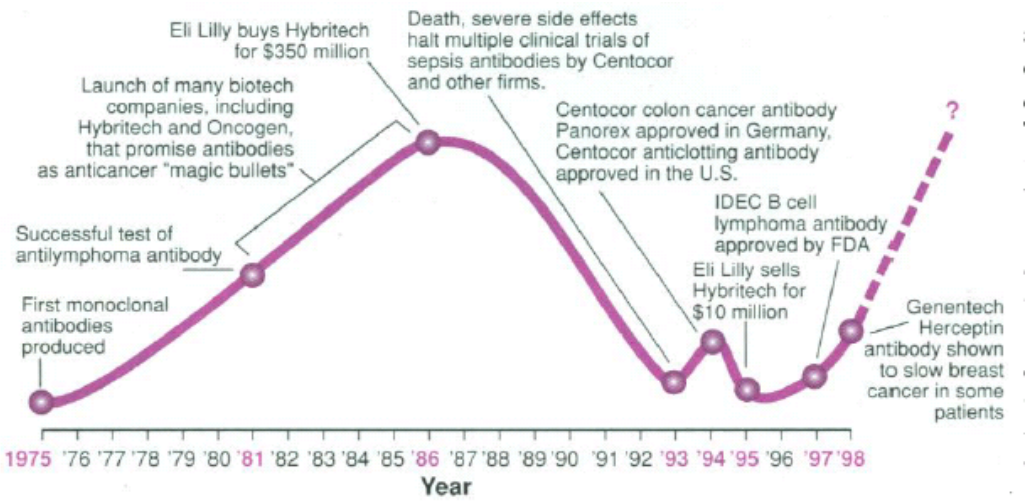


Figure 1: The ups and downs of therapeutic antibodies. Source: Dickman, S. Science. 1998:280;1186.

After years of setbacks and disappointments, recent developments have renewed optimism about the therapeutic promise of several forms of nucleic-acids drugs. Technical innovations have allowed RNA therapeutics to address problems with stability, specificity, and delivery. These advances have led to rapidly expanding pipelines and the commercialization of the first systemic RNA drug, ISIS Pharmaceuticals' Kynamro, which was approved in 2013 for the treatment of a rare, severe form of familial high cholesterol. Challenges still remain, to be sure, and the range of applications of nucleic-acid drugs is still to be determined. In the end, these therapies may not have the same clinical presence as mAb therapeutics. Nevertheless, this rapidly developing area certainly appears poised to deliver multiple important new drugs over the coming years.

THE ADVANTAGES OF NUCLEIC-ACID BASED DRUGS

Deoxyribonucleic acid (DNA) encodes the genetic material of the cell. DNA is copied into a ribonucleic acid (RNA) version through a process known as "transcription," and RNA is then "translated," or converted into protein. Traditional small-molecule drugs and mAbs generally target proteins, often with the aim of reducing their function by binding and inactivating them. In contrast, DNA or RNA nucleic-acid based drugs typically aim to decrease the levels of disease-causing proteins by reducing the levels of corresponding RNA.

RNA therapeutic approaches have several advantages relative to small-molecule drugs or mAbs. First, such compounds have the potential to be directed at so-called "undruggable targets", or classes of proteins that were otherwise difficult to drug. For example, hard-to-drug

proteins can include enzymes with highly conserved active sites that can be difficult to target specifically with small molecules without cross-reacting with other enzymes, while mAbs are largely restricted to cell-surface receptors or circulating proteins. Second, the discovery of RNA drug candidates is simpler and more rapid than other types of molecules. Because the target of RNA drugs is nucleic acid with a known sequence, drug candidates can be designed using bioinformatics, rather than via the extensive lead-optimization steps involved in the discovery and development of small molecules. The potency of specific sequences can be efficiently screened for their ability to reduce the expression of or "knock down" their target. As a frame of reference, Alnylam, a leading RNAi company, estimates programs can progress from target identification to candidate selection in a matter of weeks, a timeline markedly shorter than traditional drug development, which can take months to years. In addition, the process has a high rate of success. Note, however, that the rapidity and high hit rate of the candidate-selection process also comes with a disadvantage: promising targets validated by one nucleic-acid drug company can quickly be addressed by other companies, leading to intense competition. For instance, four companies have programs in hepatitis B, with two of them publicly announced in Q2'14. Third, companies can use particular chemical modifications to confer fairly consistent pharmacological properties across different compounds, which may reduce development times and increase success rates. Finally, companies can develop reproducible and scalable drug-manufacturing processes, which increase the efficiency of chemistry, manufacturing, and control (CMC) investments.

TYPES OF NUCLEIC-ACID THERAPEUTICS: RNA INTERFERENCE

The discovery of RNA interference (RNAi) received the Nobel Prize for Physiology or Medicine in 2006. RNAi is a naturally occurring mechanism that can reduce the expression of target genes. As with many biological pathways, the terminology of RNAi is complex. In brief, double-stranded RNA (dsRNA) is broken down into small interfering RNA (siRNA) by an enzyme called "Dicer," and the siRNA binds to RNA-induced silencing complexes (RISCs). These complexes then specifically target mRNA in a sequence-dependent manner, degrading the RNA and blocking protein synthesis. RNAi is involved in the cellular response to viruses by degrading dsRNA, which forms the genetic material of many viruses. Multiple companies are attempting to harness the RNAi pathway to reduce the expression of genes involved in a wide range of disease states.

THE UPS AND DOWNS OF THERAPEUTIC RNAi

Following the discovery of RNAi, there was tremendous excitement regarding its considerable therapeutic promise, and several biotechnology companies attempted to consolidate critical intellectual property and initiate clinical development programs. The enthusiasm over RNAi was reflected in lucrative licensing agreements, partnerships, and M&A

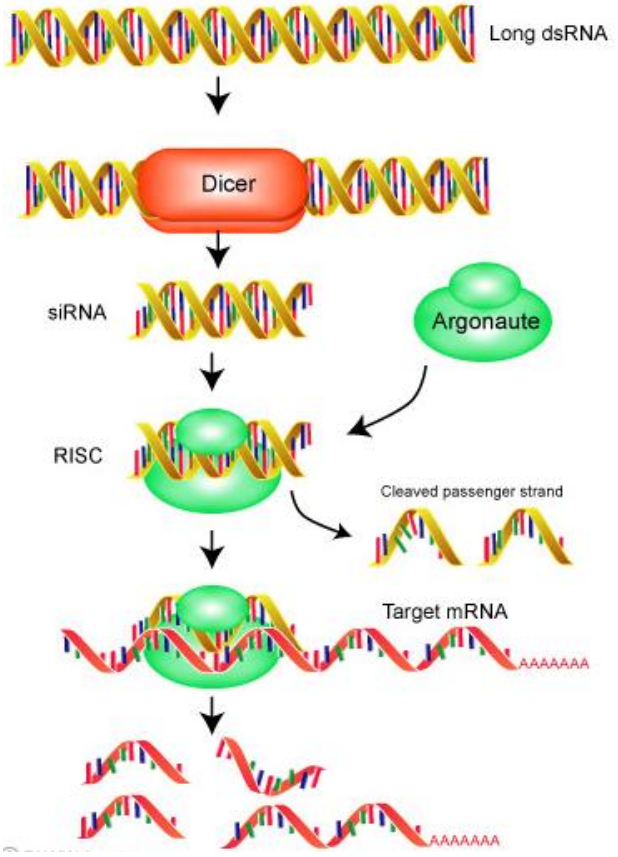


Figure 2: RNA interference. Source: RNAiweb.com.

activity between 2005 and 2008 (see figure 3). The most notable transaction was Merck's 2006 acquisition of Sirna Therapeutics for USD1.1bn – a 102% premium. However, the field encountered multiple technical challenges, the two most notable being "delivery," the ability to target RNAi drugs to the right organs or cell type to mediate their activity, and "immune stimulation," the potential to stimulate an innate immune response, which led to concerns about a lack of specificity and the risk of inflammatory side effects. The immune-stimulatory effects of RNAi are mediated through interaction with pattern-recognition receptors (PRRs), such as Toll-like receptors (TLRs), which function in immunity to microbes.

The technical setbacks caused several large pharma players to exit the RNAi space. Roche terminated its RNAi development programs in 2010, after paying USD331m upfront in 2007 for a broad partnership with Alnylam to develop drugs for cancer, respiratory diseases, metabolic disorders, and certain liver conditions, and a further USD125m for the acquisition of delivery company Mirus in 2008. Earlier in 2010, Novartis' decided not to extend its collaboration with Alnylam, which prompted Alnylam to reduce its workforce by 25-30%. (Novartis finally decided to shut down most of its RNAi operations in 2014.) Although large pharma investments may arguably be a lagging indicator of the promise of a technology, these developments led to skepticism regarding the viability of RNAi as a therapeutic modality and caused significant volatility for RNAi companies. In 2011, Alnylam shares bottomed at levels less than 20% of their previous heights in 2007-2008. In contrast to the lucrative platform deals of 2005-2008, RNAi collaborations announced in 2009-2013 were small and related to specific products, chemistries, or delivery mechanisms, and involved upfront payments under USD10m.

DATE	RNAi COMPANY	PARTNER	COMMENTS	FINANCIALS
Sept 2005	Alnylam	Novartis	Broad, 3 year research collaboration	USD10m upfront, 58.5m equity investment (~20% stake), up to USD700m in milestones + royalties
Apr 2006	Sirna	GSK	Respiratory disease	USD6m upfront, 6m equity investment, up to USD700m in milestones + royalties
Oct 2006	Sirna	Merck	Acquisition	USD1.1bn, 102% premium
Jul 2007	Silence	AstraZeneca	Up to 5 respiratory targets	USD5m upfront, 10m equity investment, up to USD385m in milestones + royalties
Jul 2007	Alnylam	Roche	Nonexclusive access to four therapeutic areas (oncology, respiratory, metabolic, some liver diseases)	USD274m upfront, 42.5m equity investment (~20% stake), up to >USD700m in milestones + royalties
May 2008	Alnylam	Takeda	Nonexclusive access to oncology and metabolic disease, rights of first refusal for Asian co-development	USD150m upfront, up to USD171m in milestones/product + royalties
Jul 2008	Mirus	Roche	Acquisition of delivery technology	USD125m
Oct 2011	Roche	Arrowhead	Acquisition of delivery technology	Up to USD9m in stock, rights of first negotiation, milestones + low single digit royalties
Jan 2014	Alnylam	Merck	Intellectual property, RNAi products, polyconjugate technology	USD175m, milestones, royalties
Jan 2014	Alnylam	Sanofi	Commercial rights outside North America and Western Europe for patisiran and several other drugs	USD700m equity investment (~12% stake), milestones + tiered double-digit royalties up to 20%

Figure 3: Select RNAi therapeutics deals. Source: Haussecker D. Molecular Therapy - Nucleic Acids. 2012:2, e8; Haussecker D. Human Gene Therapy. 2008:19;451. Company reports.

In recent years, Alnylam and other companies have made significant progress in resolving many of these challenges. Multiple delivery strategies have shown promise, particularly in targeting the liver, and while the most advanced pipeline compounds use formulations requiring intravenous infusions with concomitant steroid medication, Alnylam expects its next generation of drugs about to enter the clinic will be better tolerated and will be able to be dosed subcutaneously without steroids. It is important to note that the immune-stimulatory effects of RNAi drugs have largely been managed through chemical modifications

that reduce binding to pattern-recognition receptors. Thus, although the platform may not be as broadly applicable as was once thought, optimism about the commercialization of multiple RNAi drugs over the coming years is certainly warranted. Even though RNAi stocks have remained volatile in 2014, the fluctuations have generally mirrored small-cap biotech stocks' overall volatility and relate in part to their very strong performances in January and February. For example, while Arrowhead (Nasdaq:ARWR) and Tekmira (Nasdaq:TKMR) shares ended the second quarter down 46% and 58% from their March highs, those levels reflected over-enthusiastic investor expectations on the companies' hepatitis B programs. Still, both stocks outperformed the Nasdaq Biotechnology Index in the first half of 2014 and were up 34% and 64%, respectively.

Merck also recently decided to exit the RNAi space, and in January 2014, eight years after acquiring Sirna (but quite soon after the appointment of a new head of R&D), Merck sold its RNAi assets to Alnylam for USD175m (mainly in stock). However, the sale may relate more to corporate strategy and portfolio decisions (eg, development of specific liver-targeted drugs) than prior announcements, which were broadly interpreted as a lack of confidence in the technology. Importantly, at least some large pharma companies are investing in RNAi. In a deal also announced in January 2014, the Genzyme unit at Sanofi in-licensed commercial rights outside North America and Western Europe to several of Alnylam's lead clinical candidates. In addition to participating in development costs, milestones, and royalties, Genzyme purchased USD700m of newly issued Alnylam stock at about USD80.00/share, a 25% premium to prior trading, representing approximately 12% of the company.

RNAi COMPANIES: STRUCTURE, CHEMISTRY, AND DELIVERY TECHNOLOGIES

RNAi platforms and companies are differentiated by their RNAi structure, the chemistry of the nucleic acid, and the delivery technology. Alnylam is the leading company in RNAi, based on both market cap and clinical-development stage. Alnylam holds extensive intellectual property relating to an optimal structure of siRNA (ie, with respect to the length of nucleic acid base pairs and short single-strand overhangs at the end of the oligonucleotide [specifically, 19-21 nucleotides in length or 19-21mers, with 3' overhangs]). As discussed previously, several large pharma players have taken expensive licenses from Alnylam, and these deals testify to the strength of the company's patent estate. At the same time, other RNAi companies are developing drugs with distinct structures such as longer dsRNA without single stranded overhangs (so-called "blunt-end dsRNA"), some of which may face challenges due to lower potency.

Alnylam's most advanced clinical compound is patisiran, which is now in phase III trials for the treatment of transthyretin-related (TTR) amyloidosis. TTR amyloidosis is a debilitating and fatal disease caused by mutations in the TTR gene, which causes the formation of insoluble amyloid fibrils that accumulate in various tissues, leading to progressive sensory, motor, and autonomic impairment. Phase II trials showed drug safety, as well as the effective knockdown of TTR levels (up to 85%). The findings generated significant enthusiasm in the medical and investment communities, since mechanistically, reducing TTR protein should have a potentially profound impact on disease outcomes. However, data from the ongoing phase III trials, expected in 2016, will be the first demonstration of patisiran's effect on disease and will be key to evaluating the drug's commercial outlook, which is now widely considered to have blockbuster potential.

DISEASE	DRUG	COMPANY	TARGET	CONDITION	ADMINISTRATION	CARRIERS	siRNA MODIFICATION	TRIAL STATUS AND REMARKS
Eye-related disorders	AGN-211745	Sirna	VEGF-R1	Age-related macular degeneration; choroidal neovascularization	Intravitreal	Naked siRNA	Yes	Phase II; terminated; efects of siRNA most likely mediated via toll-like receptor activation
	QPI-1007	Quark	Caspase 2	Non-arteritic ischemic optic neuropathy (NAION)	Intravitreal	Naked siRNA	Yes	Phase I; completed
	PF-655	Quark	RTP801	Age-related macular degeneration, diabetic macular edema	Intravitreal	Naked siRNA	Yes	Phase II; ongoing
	SYL001	Sylentis	TRPV1	Ocular pain	Intravitreal	Naked siRNA	No	Phase I/II; recruiting
	SYL040012	Sylentis	b2 adrenergic receptor	Glaucoma	Intravitreal	Naked siRNA	Unknown	Phase II; completed
	Bevasiranib	Opko Health	VEGF-R1	Age-related macular degeneration, diabetic macular edema	Intravitreal	Naked siRNA	Yes	Phase III terminated due to unmet primary end point
Viral infections	TKM-100201	Tekmira	VP24, VP35, Zaire Ebola L polymerase	Ebola infections	Intravenous	LNP	Unknown	Phase I; ongoing
	ALN-RSV01	Alnylam	RSV nucleocapsid	Respiratory syncitial virus	Inhaled	Naked siRNA	Yes	Phase II; completed
	ARC -520	Arrowhead	HBV	Hepatitis B	Intravenous	DPC	Yes	Phase I; recruiting
Cancer	Atu027	Silence	PKN3	Advanced, recurrent or metastatic solid malignancies	Intravenous	LNP	Yes	Phase I; completed
	TKM-PLK1	Tekmira	PLK1	Gastrointestinal neuroendocrine tumors, adrenocortical carcinoma and hepatocellular carcinoma	Intravenous	LNP	Yes	Phase I/II; recruiting
	CALAA-01	Calando	RRM2	Solid tumors	Intravenous	Cyclodextrin NP	No	Phase I; terminated
	SiG12D LODER	Silenseed	KRAS-G12D	Pancreatic cancer	Intravenous	LODER polymer	No	Phase II; not yet recruiting; first to target undruggable mutation in cancer
	ALN-VSP02	Alnylam	VEGF, kinesin spindle protein	Solid tumors with liver involvement	Intravenous	LNP	Yes	Phase I; completed; first to report therapeutic anti-tumor response following systemic administration of siRNA
Cardiovascular diseases	ALN-PCS02	Alnylam	PCSK9	Hypercholesterolemia	Intravenous	LNP	Yes	Phase I; completed
	TKM-ApoB	Tekmira	ApoB	Hypercholesterolemia	Intravenous	LNP	Yes	Phase I; terminated; siRNA immune stimulation reaction prohibited dose escalation
Orphan diseases	ALN-TTR01	Alnylam	TTR	Transthyretin-mediated amyloidosis	Intravenous	LNP	Yes	Phase I; completed
	ALN-TTR02	Alnylam	TTR	Transthyretin-mediated amyloidosis	Intravenous	LNP	Yes	Phase III; recruiting; Phase I trial demonstrated improved delivery efficacy using second generation LNPs
	ALN-TTRsc	Alnylam	TTR	Transthyretin-mediated amyloidosis	Subcutaneous	GalNac conjugate	Yes	Phase II; ongoing
	ALN-AT3SC	Alnylam	Antithrombin (AT)	Hemophilia A or B	Subcutaneous	GalNac conjugate	Yes	Phase I; ongoing
Kidney disorders	QPI-1002	Quark	p53	Delayed graft function in kidney transplant, acute renal failure	Intravenous	Naked siRNA	Yes	Phase I/II; ongoing
Dermal scarring	RXI-109	Rxi	CTGF	Dermal scarring	Intradermal	Self-delivering	Yes	Phase I/ II; ongoing
Asthma	Excellair	Zabecor	Syk	Asthma	Inhaled	Naked siRNA	Unknown	Phase II; ongoing

Figure 4: Select RNAi drugs in clinical trials. Source: Adapted from Wu. Et al. Science Translational Medicine 2014;6:7.

Patisiran is formulated for delivery with lipid nanoparticles (LNP), a technology that enables targeting siRNA to the liver but requires intravenous drug administration and premedication with steroids. The LNP technology was developed with Tekmira; following a bitter legal dispute between the companies, Alnylam now has a license to the technology. Alnylam's more recent pipeline programs use conjugation of a sugar molecule called "GalNAc" to the siRNA, which binds to a receptor expressed on liver cells. The GalNac technology allows for subcutaneous administration, although it still requires steroids. Alnylam's demonstration of knock down with a different TTR-targeting siRNA drug in up to 40 healthy volunteers was a very significant milestone, as subcutaneous dosing enables targeting to a wider range of indications. Further optimization has led to Alnylam's "Enhanced Stabilization Chemistry" (ESC)-GalNAc-conjugate delivery platform, which has demonstrated a 10-fold increase in potency in non-human primate (NHP) studies. The approach also has the potential for once-monthly or possibly less-frequent subcutaneous dosing without steroids. Alnylam hopes to have five or more programs in the clinic by 2015, all of which use ESC-GalNac. While delivery for these and several other platforms is currently restricted to the liver, the central role of liver cells in many infectious and metabolic diseases has the potential to translate into rich pipelines despite this limitation.

The major differentiation of Arrowhead Research is its Dynamic Polyconjugates (DPCs) delivery technology (see figure 5), which Roche developed through its acquisition of Mirus for USD125m in 2008 and then divested to Arrowhead in 2011 for about USD9m. DPCs are small nanoparticles, composed of a polymer to which agents can be attached to shield the RNAi from degradation or target the particles to specific cells or organs. Particles are taken up into a cell's endosome; once inside, the polymer mediates specific release of the particle from endosomes, thereby enhancing efficiency relative to the passive diffusion seen with other platforms. DPCs are designed to increase stability of the siRNA, reduce nonspecific toxicity, and increase the efficiency of delivery. In terms of the structure and chemistry of the siRNA, Arrowhead has licensed access to three different siRNA formats and advanced chemical modifications, including Alnylam's siRNA technology and Dicerna's Dicer substrates (see below). Arrowhead's current programs target the liver and are administered intravenously, although the company has indicated

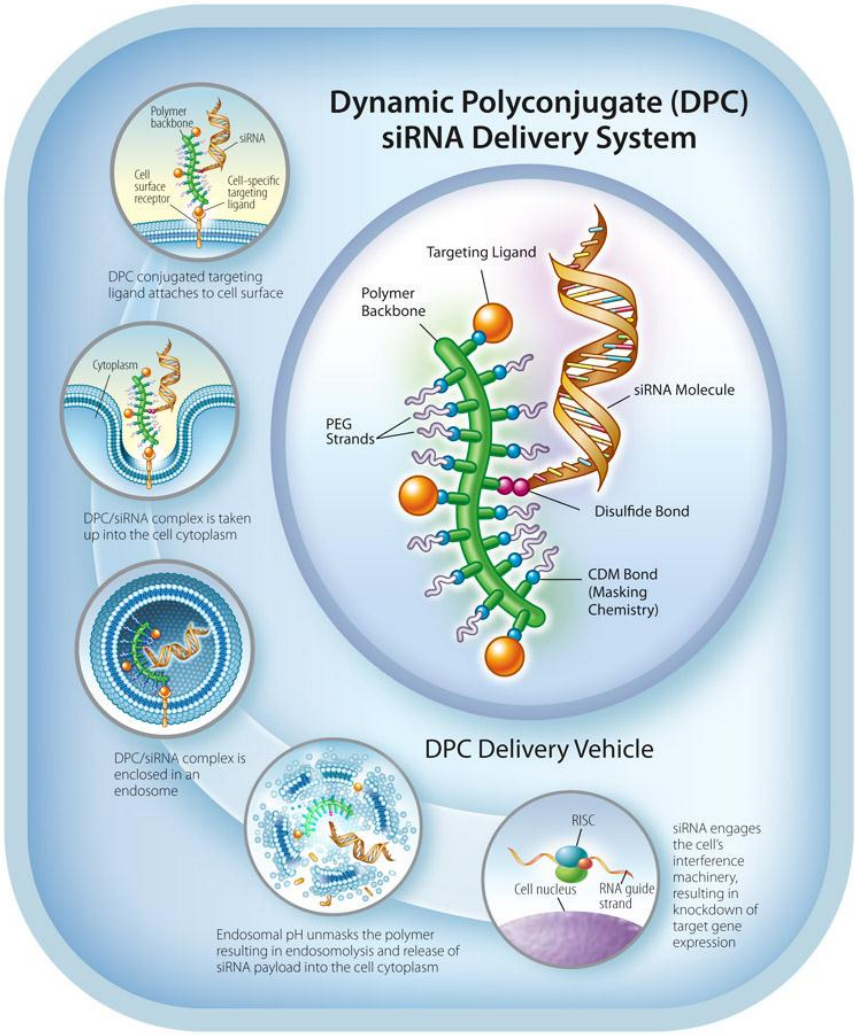


Figure 5: Dynamic polyconjugate system and mechanism of siRNA delivery. Source: Arrowhead Research.

that subcutaneous delivery is under development, which will be important for competitive positioning.

Arrowhead's lead program is in the treatment of hepatitis B (HBV), with single-dose phase II data expected later this year. In contrast to current antiviral drugs, which are taken chronically to suppress viral replication, RNA-targeting approaches have the potential to produce functional cures of HBV. If successful, this approach will represent a multibillion dollar commercial opportunity. Although several other RNA therapeutics companies have programs in HBV, including Tekmira, Isis, and Alnylam, Arrowhead is in the lead by about 9-18 months. While the program has already generated significant investor enthusiasm, additional data in humans, including multi-dose trials, will obviously be critical de-risking events for Arrowhead's platform. At an analyst event in mid-June, Arrowhead disclosed a second clinical program in Alpha-1 Antitrypsin Deficiency (AAT) associated liver disease. Not surprisingly, Alnylam also has a program for this target.

Dicerna has proprietary technology that uses Dicer Substrate siRNA (DsiRNA), potent 25-30 base-pair asymmetric dsRNA, and its Encore LNP delivery platform to target liver and tumor cells. The company's IPO in January 2014 was unusual for a few reasons. First, there was no lock-up for existing venture investors, and second, its opening performance: on the first day of trading, Dicerna closed at over 3X its IPO price (representing a market cap of over800m). Over time, shares traded down to current levels (~50% above its IPO price and a market cap of ~USD400), a price that may better reflects its pre-clinical stage of development. Dicerna's liver-specific drug candidate for primary hyperoxaluria and its tumor-directed drug targeting MYC will both enter the clinic in early 2015, as will a Kras oncology program partnered with Kyowa Kirin. These studies should generate the necessary clinical data to validate the safety and efficacy of Dicerna's platform.

As described above, Tekmira has a proprietary lipid nanoparticle (LNP) technology and a license to Alnylam's chemistry. Tekmira's lead asset is TKM-PLK-1, now in phase I/II for the treatment of advanced gastrointestinal neuroendocrine tumors or

COMPANY	TICKER	MARKET CAP (USDm)
RNAi		
Alnylam Pharmaceuticals	Nasdaq:ALNY	4,773
Arcturus Therapeutics	Private	
Arrowhead Research	Nasdaq:ARWR	742
Ascletis	Private	
Benitec Biopharma	ASX:BLT	125
Biomics Biotechnology	Private	
Dicerna	Nasdaq:DRNA	401
iTherapeutics	Private	
Marina Biotech	OTCMKTS:MRNA	11
Nano Oncology (PeptiMed)		
Quark Pharmaceuticals	Private	
RXi Pharmaceuticals	Nasdaq:RXII	42
Silence Therapeutics	LON:SLN	196
Silenseed	Private	
Somagenics	Private	
Sylentis	Private	
Tekmira Pharmaceuticals	Nasdaq:TKMR	288
Zabecor	Private	
ANTISENSE		
Antisense Therapeutics	ASX:ANP	19
Isis Pharmaceuticals	Nasdaq:ISIS	4,051
ProNAi	Private	
Santaris	Private	
EXON SKIPING		
Prosensa	Nasdaq:RNA	442
Sarepta	Nasdaq:SRPT	1,212
MICRORNA		
InteRNA Technologies	Private	
miRagen Therapeutics	Private	
Mirna Therapeutics	Private	
RaNA Therapeutics	Private	
Regulus Therapeutics	Nasdaq:RGLS	349
MESSENGER RNA		
Moderna Therapeutics	Private	

Figure 6: Companies developing nucleic-acid based drugs (market cap as of June 30, 2014). Source: Company reports, Bloomberg.

adrenocortical carcinoma. However, siRNA targeting to tumors appears less robust than to the liver, and investors are focused on Tekmira's HBV program, which is expected to generate proof-of-concept phase I data in 2015. Tekmira also has an Ebola-targeted program funded by the US government.

Several smaller RNAi companies also have clinical development programs. Quark uses blunt dsRNA licensed from Silence Therapeutics and Anylam, and has two phase II programs: PF-655 for diabetic macular edema, which is being conducted in partnership with Pfizer, and QPI-1002 for acute kidney injury and graft function, for which Novartis holds an option. RXi is developing a locally administered RNAi that targets connective tissue growth factor (CTGF); the drug currently is in phase II studies for the reduction of post-surgical scar formation. Silence Therapeutics uses blunt-end dsRNA and LNP delivery directed to the liver and vascular and pulmonary endothelium, with its lead candidate, Atu027, in phase Ib/IIa in pancreatic cancer. Silenseed, which is currently in an IPO process, uses a proprietary delivery system known as LODER (Local Drug EluterR). The company recently reported promising phase I/II data in pancreatic cancer. Finally, Benitec has a DNA-directed RNAi platform, while Marina Biotech is developing various modifications on RNAi chemistry and delivery. Additional preclinical and clinical data will be required to be able to assess the potential of these platforms and their differentiation from those of companies in more advanced clinical development. A full list of companies developing RNAi and other nucleic-acid based therapeutics can be seen in figure 6.

ANTISENSE THERAPEUTICS

Antisense drugs are single-stranded nucleic acids that can function in several ways to modulate gene expression (see figure 7). Isis Pharmaceuticals is the leading antisense company, and it has pioneered advances in chemistry that have been fundamental drivers of the field of nucleic acid therapeutics. Most of the compounds in Isis' pipeline function through binding to target RNA and forming a double stranded duplex that is recognized and degraded by an enzyme called RNAse H. Several antisense drugs can function through binding mRNA to induce alternative splicing or variants of mRNA. One example is ISIS-SMN, which aims to increase the expression of SMN for the treatment of patients with spinal muscular atrophy (SMA). Isis also has a program in which the target disease is mediated by toxic RNA; in this case, antisense-directed RNA degradation through an RNAse H-dependent mechanism could directly improve the disease (myotonic dystrophy type I).

As with other therapeutic modalities, antisense drug makers have faced significant technical challenges, especially the development of chemistries that are sufficiently stable and provide the requisite affinity for the compounds to be effective. In addition, the technologies are evolving to address non-specific immune-stimulatory effects, which are again mediated by pattern-recognition receptors, such as the Toll-like receptors (TLRs) expressed by the immune system. Thus, while the first antisense drug was approved in 1998 for the local treatment of cytomegalovirus retinitis in the eye (Isis' Vitravene), it was not until 2013 that the company received approval for a systemic therapy, Kynamro.

Several key developments were instrumental in the creation of Isis' antisense platform. These include chemistry advances, which modified the structure of the nucleotides. As a consequence, Isis' second-generation chemistry (2′-O-methoxy ethyl GAPmer oligonucleotides) is more potent and stable than its first-generation (phosporothioate) platform, even as it reduces non-specific toxicities. Most of Isis' current pipeline uses generation-2 chemistry, which can target the liver efficiently without requiring complex delivery vehicles. Such drugs can also be administered locally in a variety of organs (eg, via intraocular injection, intrathecal delivery to the central nervous system, and orally or via enema for activity in the gastrointestinal tract). Further improvements in Isis' future pipeline include increased potency [generation 2.5, 2′,4′-constrained ethyl (cEt) gapmer], as well as ligand-conjugation (LICA) technology to enhance targeting to the liver and other organs; these can reduce the amount of drug required by as much as 10-

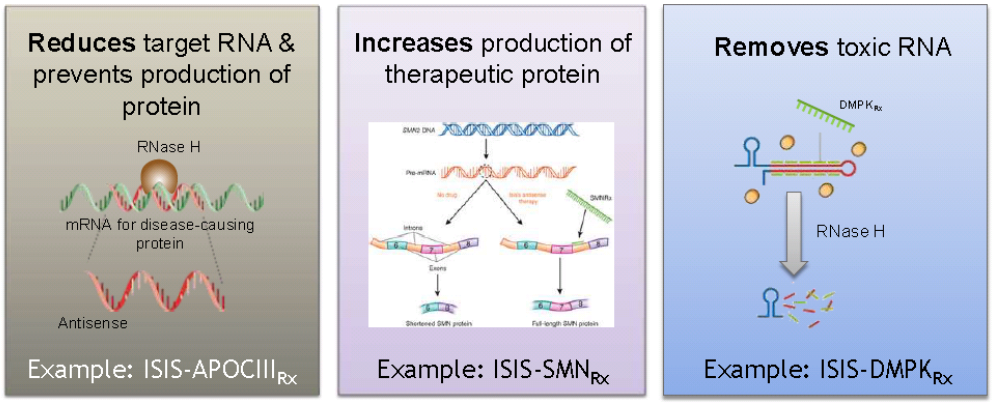


Figure 7: Multiple mechanisms underlying antisense therapeutics. Source: Isis Pharmaceuticals.

to 100-fold. Increased potency can enhance efficacy in other organs in addition to the liver, such as in tumors or the kidney, as the potency can compensate for lower drug concentrations. Isis also uses high-throughput screening to optimize its antisense oligonucleotide sequencing, which reduces the risk of non-specific inflammation and improves tolerability. Thus, its more recent pipeline candidates have significantly lower injection-site reactions than have been observed with Kynamro.

These advances have facilitated the development of Isis' extensive pipeline, which now includes more than 30 products in the clinic. Isis has been able to capitalize on the several strengths of nucleic-acid drug development: rapid, rational, and efficient drug design. Indeed, Isis typically moves from decision-on-target to clinical-candidate selection in 12 months, a timeline that includes extensive three-month non-human primate toxicology.

The programs for which investors have the highest expectations are ISIS-SMN and APOCIII. ISIS-SMN is partnered with Biogen-Idec as part of a broad collaboration across several neurology indications. ISIS-SMN is delivered by intrathecal injection into the central nervous system every few months and is poised to enter phase III trials in infants and children with SMA. SMA is characterized by progressive muscle atrophy and loss of motor function, with age of onset and severity dependent on the residual amount of SMN protein; the most severe form of the disease is fatal within a few months of birth. ISIS-SMN showed encouraging results in open-label phase II studies, demonstrating increases in SMN protein in cerebrospinal fluid and some improvement of motor function, as well as potential survival benefits relative to the natural history of the disease. Despite these findings, Isis shares have been under pressure following the most recent SMN update at April's American Association of Neurology meeting. Causes of the pushback include the difficulty of interpreting single-arm, uncontrolled trials, high investor expectations for the program and the competitive landscape which includes a small molecule from Roche and PTC Therapeutics as well as gene therapy approaches. APO-CIII is less controversial. Isis has shown exciting data for its compound targeting apolipoprotein C-III for lowering triglycerides in conditions with a high risk of pancreatitis or cardiovascular disease. The program is about to enter phase III in two orphan disease settings: familial chylomicronemia syndrome (FCS) and patients with severely high triglycerides (>880 mg/dL).

Figure 8: Antisense drugs in clinical trials. Source: Company reports.

DRUG	COMPANY	TARGET	CONDITION	ADMINISTRATION	TRIAL STATUS AND REMARKS
COMMERCIALIZED					
Kynamro	Isis/ Genzyme	ApoB	Homozygous familial hypercholesterolemia	Subcutaneous	Approved in 2013
Alicaforsen	Isis/ Atlantic	ICAM1	Pouchitis	Enema	Named patient program
Vitavene	Isis	CMV	CMV Retinitis	Intravitreal	Approved in 1998
PHASE III					
ISIS-TTR	Isis/ GSK	TTR	Transthyretin-mediated amyloidosis	Subcutaneous	Phase III; ongoing
Kynamro	Isis/ Genzyme	ApoB	Severe heterozygous familial hypercholesterolemia	Subcutaneous	Label expansion studies ongoing
Custirsen/ OGX-	Teva/ Oncogenex/ Isis	Clusterin	Prostate and lung cancer	Intravenous	Phase III; ongoing
PHASE II					
GED-0301	Nogra/ Celgene	Smad7	Crohn's disease	Oral	Phase II; completed. Data expected H2'14, phase III start H2'14
ISIS-SMN	Isis/ Biogen Idec	SMN	Spinal muscular atrophy	Intrathecal	Phase II; interim results presented, trial ongoing. Phase III start H2'14
ISIS-APOCIII	Isis	ApoCIII	Familial chylomicronemia syndrome (FCS), severely high triglycerides	Subcutaneous	Phase II; completed. Phase III start H2'14.
ISIS-GCGR	Isis	Glucagon receptor	Diabetes	Subcutaneous	Phase IIa; completed.
ISIS-GCCR	Isis	Glucocorticoid receptor	Diabetes	Subcutaneous	Phase II; ongoing.
ISIS-FXI	Isis	FactorXI	Clotting disorders	Subcutaneous	Phase II; ongoing.
ISIS-CRP	Isis	CRP	Coronary artery disease	Subcutaneous	Phase II; ongoing.
ISIS-PTP1B	Isis	PTB1B	Diabetes	Subcutaneous	Phase II; ongoing.
ISIS-EIF4E	Isis	Eukaryotic initiation factor-4e	Cancer	Subcutaneous	Phase II; ongoing.
ISIS-STAT3	Isis/ AstraZeneca	STAT3	Lymphoma (DLBCL), hepatocellular carcinoma	Subcutaneous	Phase I/II; ongoing.
Apatorsen/ OGX-427	Oncogenex/ Isis	Hsp27	Multiple cancers	Intravenous	Phase II; ongoing.
PNT2258	Pronai	Bcl-2	Non-Hodgkin's lymphoma	Intravenous	Phase II; ongoing. Promising interim results have been presented.
SPC2968	Santaris	Hif-1 alpha	Hepatocellular carcinoma, head and neck squamous cell carcinoma	Subcutaneous	Phase II; ongoing.
ATL-1103	Antisense/ Isis	Growth hormone receptor	Acromegaly	Subcutaneous	Phase II; ongoing, recruitment completed.
ATL-1102	Antisense/ Isis	VLA4	Multiple sclerosis	Subcutaneous	Phase IIa; completed.
EXC001	Pfizer/Isis	Connective tissue growth factor	Scarring	Local skin	Phase II; ongoing.
iCo-007	iCo/Isis	c-raf	Diabetic macular edema	Intravitreal	Phase II; ongoing.
PHASE I					
ISIS-AR	Isis/ AstraZeneca	Androgen receptor	Prostate cancer	Subcutaneous	Phase I; ongoing.
ISIS-APO(a)	Isis	APO(a)	Cardiovascular disease	Subcutaneous	Phase I; ongoing.
ISIS-ANGPTL3	Isis	ANGPTL3	Hyperlipidemia	Subcutaneous	Phase I; ongoing.
ISIS-PKK	Isis	Prekallikren	Hereditary angioedema	Subcutaneous	Phase I; ongoing.
ISIS-DMPK	Isis/ Biogen Idec	Dystrophia myotonica-protein kinase	Myotonic Dystrophy Type 1	Subcutaneous	Phase I; ongoing.
ISIS-HBV	Isis/ GSK	HBV	Hepatitis B	Subcutaneous	Phase I; ongoing.
ISIS-FGFR4	Isis	FGFR4	Obesity	Subcutaneous	Phase I; ongoing.
AVI-7288	Sarepta	Marburg virus nucleocapsid	Marburg virus	Intravenous	Phase I; ongoing. With US Department of Defense.
AVI-7537	Sarepta	Ebola virus	Ebola virus	Intravenous	Phase I; withdrawn.
AVI-7100	Sarepta	Influenza	Influenza	Intravenous	Phase I; ongoing. With National Institutes of Health.

Investors have low expectations for Isis' phase III program targeting TTR, which is part of a collaboration with GSK across several rare and infectious-disease programs. The skepticism stems from the compound's perceived lower potency relative to Alnylam's drug, despite phase I data showing >75% average reduction of TTR (and up to 90% reduction in some subjects). Further, the commercial potential for Isis' approved drug Kynamro is limited by its tolerability and the competitive landscape, which includes Aegerion's Juxtapid, an oral drug approved for homozygous familial hypercholesterolemia, and the promising PCSK9 antibodies under development for the treatment of other settings of high cholesterol by such players as Amgen, Sanofi/Regeneron, and Pfizer.

Given the breadth of Isis' pipeline, clearly not all of its compounds need to succeed clinically or commercially to validate Isis' platform and strategy. Other programs with significant commercial potential include those targeting STAT3 and androgen receptors in cancer (both partnered with AstraZeneca), and the glucagon receptor in diabetes, which showed impressive reductions in HbA1c of up to 2.25% at 13 weeks, although concerns about increases in liver enzymes may limit development to patients with the highest unmet need. Although this market is large, investors may await the program's

validation through a commercial partnership before assigning much value to the program.

A striking antisense deal was announced by Celgene in April 2014. The terms included a staggering upfront of USD710m, in addition to as much as USD815m in regulatory and development milestones and USD1050m in sales milestones and tiered royalties. Celgene in-licensed GED-0301, an oral antisense DNA oligonucleotide targeting Smad7 for the treatment of Crohn's disease and other indications, from Nogra Pharma, a little-known private biotech based in Ireland. While the drug is promising, only extremely early phase I data are publicly available; phase II results will be presented later this year, and Celgene plans to initiate a phase III registration program by the end of 2014. It should be noted that GED-0301 is a simple first-generation phosphorothioate DNA oligonucleotide, dosed orally via an enteric coated tablet to act locally in the intestines. This suggests Celgene invested in the specific drug and not more broadly in an antisense technology.

Other antisense companies are developing differentiated chemistry; these include Santaris, a private company working on a locked nucleic-acid (LNA) platform, which enables high-affinity binding with short oligonucleotides that can be directed to several target organs by a variety of conjugations. Santaris has a compound targeting Hif-1alpha in phase II studies in solid tumors. The company has multiple pharma partners, announcing two platform deals in January 2014. The financial terms of the partnership with GSK were not released, while that with Roche involves many targets with a modest upfront payment of USD10m but royalties on up to USD138m in pre-clinical, clinical, regulatory, and sales milestones per product. It also includes funding of ongoing discovery and research activities. Santaris is collaborating with Bristol-Myers Squibb and Shire as well.

A private company called ProNAi Therapeutics is taking a differentiated approach to nucleic-acid based therapeutics with its DNA interference technology (DNAi). The platform uses single-stranded 24-mer DNA oligonucleotides to modulate gene expression by targeting the 5' prime-promoter region of genes. (The drug is delivered via an in-licensed liposomal technology.) DNAi may have an advantage relative to RNA-based approaches, as only one or two copies of DNA is targeted; in contrast, RNA is continually synthesized. ProNai's strategy could potentially translate into a low-dose and wide-therapeutic window. The company's lead compound, PNT2258, targets bcl-2, the same target as AbbVie and Roche's ABT-199, which has generated encouraging data in chronic lymphocytic leukemia. PNT2258 has also shown promising interim phase II results, with an overall response rate of 40% in patients with follicular lymphoma (FL) and 50% in patients with diffuse large B-cell lymphoma (DLBCL). ProNAi also has multiple preclinical DNAi programs in oncology.

Two other preclinical-stage, private antisense companies are Isarna, which is developing TGF-beta inhibitors to stimulate the immune system for indications including oncology, and RaNa, which licensed Santaris technology for up to 10 targets across a range of indications. A full list of antisense drugs in clinical development can be seen in figure 8.

EXON SKIPPING

A specific application of antisense technology is exon skipping, which is being developed for the treatment of Duchenne's muscular dystrophy (DMD). DMD, a severe, progressive, and invariably fatal neurodegenerative disease, is caused by mutations in the dystrophin gene, which impairs the production of functional protein. Exon skipping uses antisense oligonucleotides that target specific dystrophin mutations in subsets of boys affected with DMD. In so doing, a specific gene segment or exon is 'skipped' to result in the generation of a shorter, but still functional, RNA. In this way, exon-skipping technologies may be able to reduce DMD symptoms and disease severity, mimicking the naturally occurring, milder condition of Becker muscular dystrophy.

Two companies are developing exon-skipping platforms for the treatment of DMD. Sarepta's technology platform involves intravenous administration of phosphorodiamidate morpholino

oligomer (PMO) chemistry which was optimized for high affinity and low immune stimulatory effects. The company has shown early, albeit promising, results in an open-label trial of its lead compound eteplirsen in 12 boys with DMD. Eteplirsen targets exon 51 and is relevant for about 13% of boys with DMD. Sarepta is also developing antisense PMO compounds for several infectious diseases.

Prosensa uses distinct 2' O-methyl phosphorothioate chemistry administered subcutaneously and has had a more mixed data set with their lead compound drisapersen, which targets the same exon as eteplirsen. Despite strong phase II data, drisapersen failed in phase III, which may have been in part due to sub-optimal trial design – the study began before recent insights into the natural history of DMD were gleaned. More specifically, the trial included both boys whose disease was too advanced to benefit from the drug, as well as those who were in the earlier stages of disease and may have been unable to show a drug benefit.

In light of the unmet need in DMD, the promising findings on walking ability (assessed by the 6-minute walk test), and some data showing restoration of dystrophin expression, the FDA will permit both Sarepta and Prosensa to file for accelerated approval, with full approval following additional confirmatory trials. Both companies expect to file in the US in the second half of 2014. Prosensa will also file for accelerated approval in the EU; although both companies appear to have freedom to operate in the US, issued patents prevent Sarepta from the EU markets for drugs targeting exon 51 and one additional exon. Sarepta and Prosensa both have additional clinical and preclinical programs targeting mutations that affect about 50% of patients with DMD. As with other antisense drugs, clinical development may be expedited by similar pharmacological properties of different candidates.

MICRORNA

MicroRNAs are small, 20-25 nucleotide naturally occurring RNA molecules that control cellular processes or pathways of gene expression. Nearly 700 microRNAs have been identified in humans. Each can regulate the expression of hundreds of genes and may be dysregulated in conditions including cancer, inflammation, fibrosis, and metabolic disease.

Several companies are attempting to regulate disease-causing pathways via microRNA. Regulus Therapeutics, formed in 2007 by Isis and Alnylam, has access to an enormous patent estate on microRNA technologies and chemistries. Regulus is developing "anti-miRs," which antagonize the function of microRNA. Anti-miRs distribute broadly in multiple tissues and do not require a specialized formulation or delivery vehicle. The company is targeting upregulated microRNAs in a number of indications, with its lead candidate about to enter phase I in hepatitis C. Regulus has multiple proprietary programs, as well as partnerships with GSK and AstraZeneca.

Two private microRNA companies are Mirna Therapeutics, which is focused on oncology, and MiRagen, which hopes to address cardiovascular disease (partnered with Servier), metabolic disease and fibrosis. The former company has a clinical candidate in phase I for patients with liver cancer or liver metastases, and a pipeline of eight microRNAs for various oncology indications, while the latter is still in the pre-clinical stages of drug development.

MESSENGER RNA THERAPEUTICS

In contrast to RNAi and antisense approaches that knock down gene expression, a private company called Moderna is developing a novel approach using messenger RNA therapeutics. Here, the objective is to introduce nucleic acid drugs into patient cells to induce the production of specific proteins. Although little is publicly known about the drug platform, Moderna has attracted a great deal of attention because of the enormous promise of the platform and its highly lucrative strategic agreements. Moderna announced an agreement with AstraZeneca in March 2013, which contains a USD240m upfront payment for a five-year option agreement on up to 40 medicines in cardiometabolic diseases and selected oncology targets. In another deal announced in January 2014,

Alexion paid USD100m upfront and made an equity investment of USD25m for options on ten preclinical programs in rare diseases. Both agreements also entail development and commercial milestones, and royalties on commercial sales.

Moderna claims a broad intellectual-property estate, chemistry enabling stable mRNA that only minimally stimulate an innate immune response, and efficient translation of dozens of proteins in a myriad of cell types via intra-muscular, subcutaneous, and intravenous administration. Messenger RNA therapeutics certainly has the potential to be a disruptive technology, and clinical development will be followed closely.

CONCLUSIONS

Advances in the stability, specificity, and delivery of nucleic-acid-based therapeutics, coupled with rational, rapid, and efficient drug design have led to extensive RNAi and antisense drug pipelines. Some of the exciting candidates in clinical development include treatments for TTR amyloidosis, HBV, spinal muscular atrophy, and hypertriglyceridemia. Clinical data demonstrating safety, tolerability, and potency will be critical to de-risk these technology platforms, particularly in light of historical and ongoing challenges in the field, not to mention the routine risks inherent in drug development the companies face.

Remaining questions and risks for nucleic-acid drugs include their long-term safety and tolerability, and ability to target organs other than liver. Further, the ability to rapidly and rationally design drug candidates may accelerate competition among RNA therapeutics companies. It remains to be demonstrated whether multiple platforms will lead to effective and safe drugs or whether a single technology will win out, with respect to structure, chemistry, or RNAi delivery.

Clinical data are of paramount importance in allowing investors to gauge the ability of a promising platform to translate into significant therapeutic benefits and commercial opportunities; it is difficult to accurately predict success based on even exciting preclinical data given the challenges described above. Therefore, companies with the most advanced clinical programs, such as Alnylam and Isis, with their strong intellectual property, coherent drug development strategies, and multiple shots on goal currently appear best positioned to realize the potential of nucleic-acid therapeutics.

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