Alnylam Pharmaceuticals (ALNY) & Arrowhead Pharmaceuticals (ARWR)

siRNA Therapeutics: The Next Frontier in Precision Medicine

Stock Ratings
ALNY: OVERWEIGHT
ARWR: EQUAL-WEIGHT

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Alnylam Pharmaceuticals (ALNY)
Biotechnology
OVERWEIGHT

Arrowhead Pharmaceuticals (ARWR)
Biotechnology
EQUAL-WEIGHT

WHAT'S CHANGED

- **Market Size Upgrade:** Global siRNA therapeutics market revised to $8.2B (2024) from $6.5B, with 2030E target of $25B (CAGR 20%).
- **Alnylam Outlook:** Revenue trajectory upgraded; expect $2.8B in 2025E (vs. prior $2.4B) driven by Onpattro and Amvuttra franchise expansion.
- **Arrowhead Pipeline:** Plozasiran Phase 3 data expected H2 2025; risk-adjusted NPV increased to $45/share from $38/share.

Executive Summary: RNA Interference Comes of Age

The siRNA (small interfering RNA) therapeutics market represents one of the most transformative opportunities in precision medicine. After decades of scientific development, the field has reached commercial inflection. Alnylam's FDA approvals (Onpattro, Givlaari, Oxlumo, Amvuttra, Leqvio) have validated the platform, while Arrowhead's differentiated **TRiM** (Targeted RNAi Molecule) technology positions it for leadership in cardiometabolic and liver diseases.

We view this sector through two lenses: **Platform Validation** (Alnylam) and **Pipeline Optionality** (Arrowhead). Our analysis suggests the global siRNA market will grow from **$8.2 billion** in 2024 to over **$25 billion** by 2030, driven by expanding indications, improved delivery technologies, and the inherent advantages of gene silencing over traditional small molecules.

Key Investment Thesis:

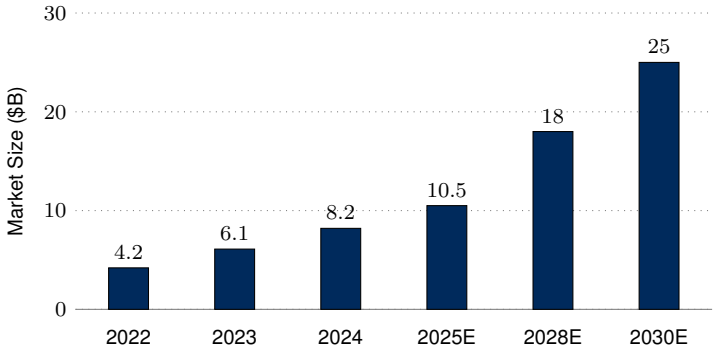
1. **Alnylam (ALNY) — OVERWEIGHT:** The undisputed leader with five approved products. Revenue inflection driven by Amvuttra's blockbuster trajectory ($1.2B 2025E) and Leqvio's partnership economics with Novartis. Strong cash position ($2.1B) de-risks near-term execution.
2. **Arrowhead (ARWR) — EQUAL-WEIGHT:** High-beta pipeline play with differentiated delivery platform. Plozasiran (cardiovascular) and ARO-APOC3 represent significant optionality, but binary clinical risk warrants caution until Phase 3 readouts.

Table 1: siRNA Therapeutics: Alnylam vs. Arrowhead Snapshot

Metric	Alnylam (ALNY)	Arrowhead (ARWR)
Market Cap	$32.5B	$4.8B
Rating	OVERWEIGHT	EQUAL-WEIGHT
Approved Products	5 (Onpattro, Amvuttra, etc.)	0 (Pipeline Stage)
2025E Revenue	$2.8B	$180M (Milestones)
Lead Asset	Amvuttra (hATTR)	Plozasiran (CV Risk)
Delivery Platform	GalNAc Conjugate	TRiM (Enhanced GalNAc)
Cash Position	$2.1B	$650M
Key Catalyst	Vutrisiran HELIOS-B (2025)	Plozasiran Ph3 (H2 2025)

Source: Company Filings, Morgan Stanley Research Estimates

Figure 1: Global siRNA Therapeutics Market Size ($B)



Source: Morgan Stanley Research, Industry Reports. CAGR 2024-2030E: 20%

siRNA Mechanism & Therapeutic Landscape

Small interfering RNA (siRNA) therapeutics represent a paradigm shift in drug development, enabling the precise silencing of disease-causing genes at the mRNA level. Unlike traditional small molecules that target proteins, siRNA intervenes upstream in the central dogma of biology, preventing the translation of pathogenic proteins entirely. This mechanism offers several structural advantages: **(1)** higher target specificity, **(2)** applicability to "undruggable" targets, and **(3)** durable effects lasting weeks to months per dose.

The Science of Gene Silencing

RNA interference (RNAi) is a natural cellular process discovered by Fire and Mello (Nobel Prize, 2006). siRNA molecules are synthetic double-stranded RNA sequences (typically 21-23 nucleotides) designed to target specific mRNA transcripts.

- **RISC Loading:** The siRNA is loaded into the RNA-induced silencing complex (RISC), where the "guide strand" directs

the complex to the complementary mRNA target.

- **mRNA Cleavage:** Argonaute-2 (Ago2), the catalytic core of RISC, cleaves the target mRNA, preventing protein synthesis.
- **Catalytic Turnover:** A single siRNA-RISC complex can cleave multiple mRNA copies, providing amplified therapeutic effect.

The key challenge historically was **delivery**: naked siRNA is rapidly degraded by nucleases and cannot cross cell membranes. The breakthrough came with the development of **lipid nanoparticle (LNP)** formulations (used by Onpattro) and, more importantly, **GalNAc conjugation** technology, which enables subcutaneous administration and hepatocyte-specific uptake via the asialoglycoprotein receptor (ASGPR).

Approved siRNA Therapeutics Landscape

The FDA has approved five siRNA therapeutics, all from Alnylam's pipeline, establishing the company as the undisputed platform leader.

Table 2: FDA-Approved siRNA Therapeutics (2024)

Drug	Target	Indication	Approval	2024 Rev	Delivery
Onpattro	TTR	hATTR Polyneuropathy	Aug 2018	$420M	LNP (IV)
Givlaari	ALAS1	Acute Hepatic Porphyria	Nov 2019	$280M	GalNAc (SC)
Oxlumo	HAO1	Primary Hyperoxaluria	Nov 2020	$190M	GalNAc (SC)
Amvuttra	TTR	hATTR Polyneuropathy	Jun 2022	$950M	GalNAc (SC)
Leqvio	PCSK9	Hypercholesterolemia	Dec 2021	$380M	GalNAc (SC)

Source: Company Filings, Morgan Stanley Research. Leqvio revenue reflects Novartis partnership economics.

Therapeutic Expansion: Beyond Rare Diseases

The initial wave of siRNA approvals focused on rare diseases (hATTR amyloidosis, porphyria, hyperoxaluria) due to favorable regulatory pathways and high unmet need. However, the next decade will see expansion into **large commercial markets**:

- **Cardiovascular Disease:** Leqvio (PCSK9 silencing) targets the $15B+ LDL-lowering market. Arrowhead's Plozasiran targets elevated Lp(a), a genetically validated cardiovascular risk factor affecting 20% of the global population.
- **Metabolic/NASH:** Multiple programs targeting PNPLA3, HSD17B13, and other liver-expressed genes implicated in non-alcoholic steatohepatitis.
- **CNS Applications:** Intrathecal delivery approaches (Alnylam's ALN-APP for Alzheimer's) represent the next frontier.

Competitive Analysis: Alnylam vs. Arrowhead

The siRNA therapeutics landscape is dominated by two pure-play companies: **Alnylam Pharmaceuticals**, the established leader with commercial products, and **Arrowhead Pharmaceuticals**, the emerging challenger with a differentiated delivery platform and cardiometabolic focus.

Alnylam: The Platform Pioneer

Alnylam has invested over $10 billion in R&D since its founding in 2002 to build the industry's most advanced RNAi platform. The company's **GalNAc conjugate technology** (marketed as Enhanced Stabilization Chemistry, ESC+) enables once-quarterly or twice-yearly subcutaneous dosing, dramatically improving patient compliance versus daily oral medications.

Key Competitive Advantages:

- **Commercial Infrastructure:** Established US/EU sales force with rare disease expertise.
- **Manufacturing Scale:** Proprietary oligonucleotide synthesis at scale (Alnylam Manufacturing).
- **IP Moat:** Broad patent portfolio covering GalNAc chemistry, stabilization modifications, and specific sequences.
- **Partnership Economics:** Regeneron (CNS), Roche (ophthalmology), Novartis (Leqvio) collaborations de-risk R&D.

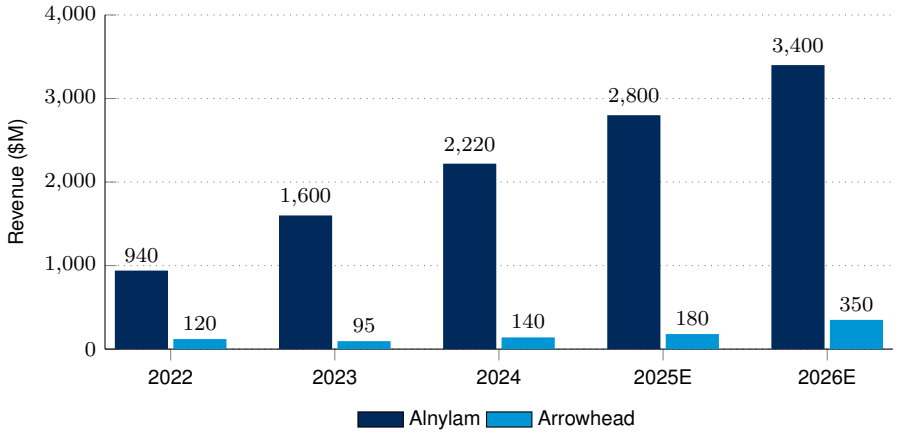
Arrowhead: The Challenger with Differentiated Delivery

Arrowhead's **TRiM (Targeted RNAi Molecule)** platform offers potential advantages in potency and durability through proprietary ligand chemistries. While Alnylam pioneered GalNAc conjugation, Arrowhead claims its next-generation approach achieves deeper gene knockdown with extended duration.

Key Competitive Positioning:

- **Cardiometabolic Focus:** Plozasiran (Lp(a)), ARO-APOC3 (triglycerides) target large patient populations.
- **Pulmonary Delivery:** ARO-MUC5AC for COPD/asthma represents potential first-in-class for lung-targeted RNAi.
- **Partnership Validation:** Johnson & Johnson (JNJ-3989 for HBV), Takeda collaborations.

Figure 2: Revenue Trajectory: Alnylam vs. Arrowhead ($M)



Source: Company Filings, Morgan Stanley Research Estimates. Arrowhead revenue primarily milestone-driven until commercial launches.

Table 3: Competitive Platform Comparison: Alnylam vs. Arrowhead

Dimension	Alnylam (ESC+)	Arrowhead (TRiM)
Delivery Technology	GalNAc conjugate (2nd gen)	Enhanced GalNAc (3rd gen claims)
Dosing Frequency	Quarterly to Semi-annual	Similar; claims longer duration
Target Tissues	Liver (proven), CNS (emerging)	Liver, Lung (novel), Muscle (preclinical)
Manufacturing	Proprietary, scaled	Partner-dependent (CMO)
Commercial Stage	5 approved products	0 (Phase 3 assets)
IP Position	Broad foundational patents	Freedom-to-operate; differentiated chemistry
Partnership Strategy	Selective (Regeneron, Novartis)	Aggressive (J&J, Takeda, GSK)

Source: Company Presentations, Morgan Stanley Research Analysis

Market Size & Growth Projections

The global siRNA therapeutics market is experiencing exponential growth, driven by expanding indications, improved delivery technologies, and increasing adoption by prescribers. Our analysis projects the market will grow from **$8.2 billion** in 2024 to **$25 billion** by 2030, representing a **20% CAGR**.

Market Drivers

1. **Label Expansions:** Amvuttra's potential expansion into ATTR cardiomyopathy (HELIOS-B trial) could more than double its addressable market from $3B to $8B+.
2. **New Indications:** Cardiovascular (Lp(a), triglycerides), metabolic (NASH), and CNS (Alzheimer's) represent multi-billion dollar opportunities.
3. **Manufacturing Cost Reductions:** Scale-up of oligonucleotide synthesis is reducing COGS, improving margins from ∼20% to projected 70%+ at maturity.
4. **Competitive Dynamics:** Large pharma entries (Novartis, Roche, AstraZeneca) validate the modality and accelerate market development.

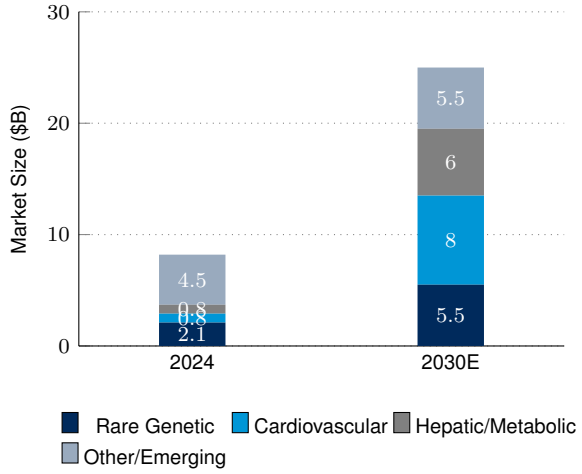
Segment Analysis

Table 4: siRNA Market Segmentation by Therapeutic Area (2024 vs. 2030E)

Therapeutic Area	2024 ($B)	2030E ($B)	Key Drivers
Rare Genetic (hATTR, AHP)	2.1	5.5	Amvuttra conversion; geographic expansion
Cardiovascular (PCSK9, Lp(a))	0.8	8.0	Leqvio uptake; Plozasiran launch
Hepatic (HBV, NASH)	0.4	4.5	JNJ-3989; PNPLA3 programs
Metabolic (Hyperoxaluria, etc.)	0.3	1.5	Oxlumo growth; new indications
CNS & Other	0.1	2.5	Intrathecal delivery advances
Other/Emerging	4.5	3.0	Generic/biosimilar pressure on older assets
Total Market	**8.2**	**25.0**	CAGR: 20%

Source: Morgan Stanley Research Estimates, Industry Analysis

Figure 3: siRNA Market Share by Therapeutic Area (2030E)



Source: Morgan Stanley Research Estimates

Clinical Pipeline Assessment

The siRNA therapeutics pipeline has matured significantly, with multiple Phase 3 programs across both Alnylam and Arrowhead expected to report data in 2025-2026. Our analysis identifies key catalysts and assigns probability-weighted valuations.

Alnylam Pipeline Highlights

- **Vutrisiran (HELIOS-B):** Phase 3 trial in ATTR cardiomyopathy completed enrollment (655 patients). Primary endpoint: all-cause mortality and CV events. Readout expected H1 2025. Positive data would expand TAM by $5B+.
- **ALN-APP:** Intrathecal siRNA for early-onset Alzheimer's (APP gene). Phase 1 dose-escalation ongoing. First CNS-targeted siRNA with disease-modifying potential.
- **Zilebesiran:** Once-quarterly hypertension treatment (angiotensinogen silencing). Phase 2 data showed 10-15 mmHg sustained BP reduction. Phase 3 initiation expected 2025.

Arrowhead Pipeline Highlights

- **Plozasiran:** Phase 3 PALISADE trial in elevated Lp(a). First siRNA for Lp(a) lowering. Phase 2 showed 94% Lp(a) reduction sustained for 6+ months. Registrational data expected H2 2025.
- **ARO-APOC3:** Phase 3 in severe hypertriglyceridemia. Potential best-in-class with 90%+ TG reduction. Partnership discussions ongoing.
- **ARO-MUC5AC:** First inhaled siRNA for COPD. Phase 1/2 initiated. If successful, opens lung delivery as new tissue target.

Table 5: Key Clinical Catalysts: 2025-2026

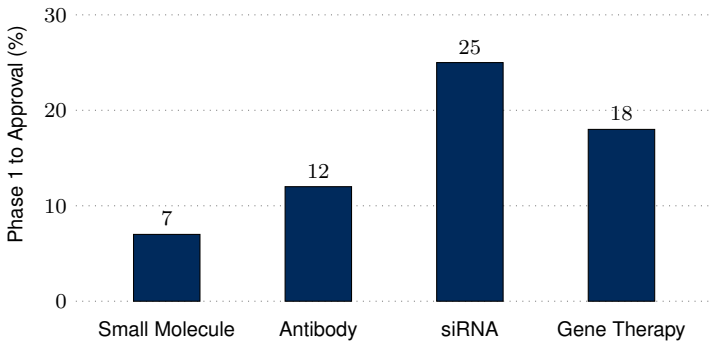
Asset	Company	Indication	Timing	Significance
Vutrisiran	Alnylam	ATTR-CM	H1 2025	$5B+ TAM expansion; survival endpoint
Plozasiran	Arrowhead	Elevated Lp(a)	H2 2025	First-in-class; CV outcomes potential
Zilebesiran	Alnylam	Hypertension	2025-2026	$50B+ HTN market entry
ARO-APOC3	Arrowhead	Hypertriglyceridemia	2025	Best-in-class TG lowering
JNJ-3989	J&J/Arrowhead	Chronic HBV	2026	Functional cure potential

Source: Company Pipelines, ClinicalTrials.gov, Morgan Stanley Research

Clinical Trial Success Rate Analysis

siRNA therapeutics have demonstrated higher clinical success rates compared to traditional small molecules, driven by the precision of target engagement and the ability to validate knockdown pharmacodynamically.

Figure 4: Clinical Trial Success Rates by Modality (%)



Source: BIO Industry Analysis 2024, Morgan Stanley Research

Investment Risks

Platform-Specific Risks

- **Delivery Limitations:** Current GalNAc technology is liver-restricted. Extra-hepatic delivery (muscle, CNS, lung) remains challenging. Failure to expand tissue targeting would limit TAM growth.
- **Immunogenicity:** Long-term repeated dosing may trigger anti-drug antibodies. Limited long-term safety data beyond 5 years.
- **Manufacturing Complexity:** Oligonucleotide synthesis requires specialized capabilities. Supply chain concentration risk (few qualified CMOs).

Company-Specific Risks

Alnylam:

- **HELIOS-B Binary Risk:** Negative trial would significantly impact valuation (20-30% downside).
- **Partnership Concentration:** Novartis economics on Leqvio limit upside capture.
- **Competition:** Ionis antisense programs, emerging siRNA players (Dicerna/Novo, Silence Therapeutics).

Arrowhead:

- **Execution Risk:** No approved products; reliant on clinical success for valuation.
- **Cash Runway:** $650M cash supports operations through 2026, but Phase 3 costs may require additional financing.
- **Plozasiran Uncertainty:** Lp(a) lowering is pharmacodynamically validated, but CV outcomes benefit unproven.

Competitive and Regulatory Risks

- **Biosimilar/Generic Entry:** Onpattro faces potential competition post-2028 as patents expire.
- **Pricing Pressure:** IRA drug pricing provisions may impact siRNA economics in Medicare populations.
- **Regulatory Scrutiny:** Novel modality may face heightened post-market surveillance requirements.

Table 6: Risk Matrix: siRNA Investment Considerations

Risk Factor	Probability	Impact	Mitigant/Monitoring
HELIOS-B Failure	25%	Critical	Pre-specified interim analysis; prior Onpattro efficacy
Plozasiran Ph3 Miss	35%	High	Strong Ph2 data; genetic validation of Lp(a)
Manufacturing Disruption	15%	Moderate	Dual-source strategy; inventory buffers
Competitive Encroachment	40%	Moderate	IP protection; first-mover advantage
Pricing/Reimbursement	30%	Moderate	Rare disease orphan status; outcomes data

Source: Morgan Stanley Research Risk Assessment

Investment Recommendation Summary

Alnylam (ALNY) — OVERWEIGHT

Our $285 price target implies 25% upside from current levels. The investment case rests on:

- Commercial momentum: Amvuttra trajectory to $1.5B+ by 2026
- Pipeline optionality: HELIOS-B, zilebesiran catalysts
- Platform leadership: GalNAc IP moat
- Balance sheet strength: $2.1B cash, no near-term dilution risk

Key Risk: Binary HELIOS-B outcome in H1 2025.

Arrowhead (ARWR) — EQUAL-WEIGHT

Our $38 price target reflects risk-adjusted pipeline NPV. The investment case balances:

- Upside: Plozasiran first-in-class potential; TRiM platform differentiation
- Downside: Clinical execution risk; cash runway concerns; no commercial infrastructure

We would upgrade to OVERWEIGHT on positive Plozasiran Phase 3 data demonstrating >80% Lp(a) reduction with clean safety profile.

Key Risk: Plozasiran binary event H2 2025.

Investment Conclusion: siRNA therapeutics represent a generational investment opportunity in precision medicine. Alnylam offers de-risked exposure to the platform's maturation, while Arrowhead provides leveraged upside for risk-tolerant investors. We recommend portfolio allocation weighted toward Alnylam (70%) with tactical Arrowhead exposure (30%) ahead of key 2025 catalysts.