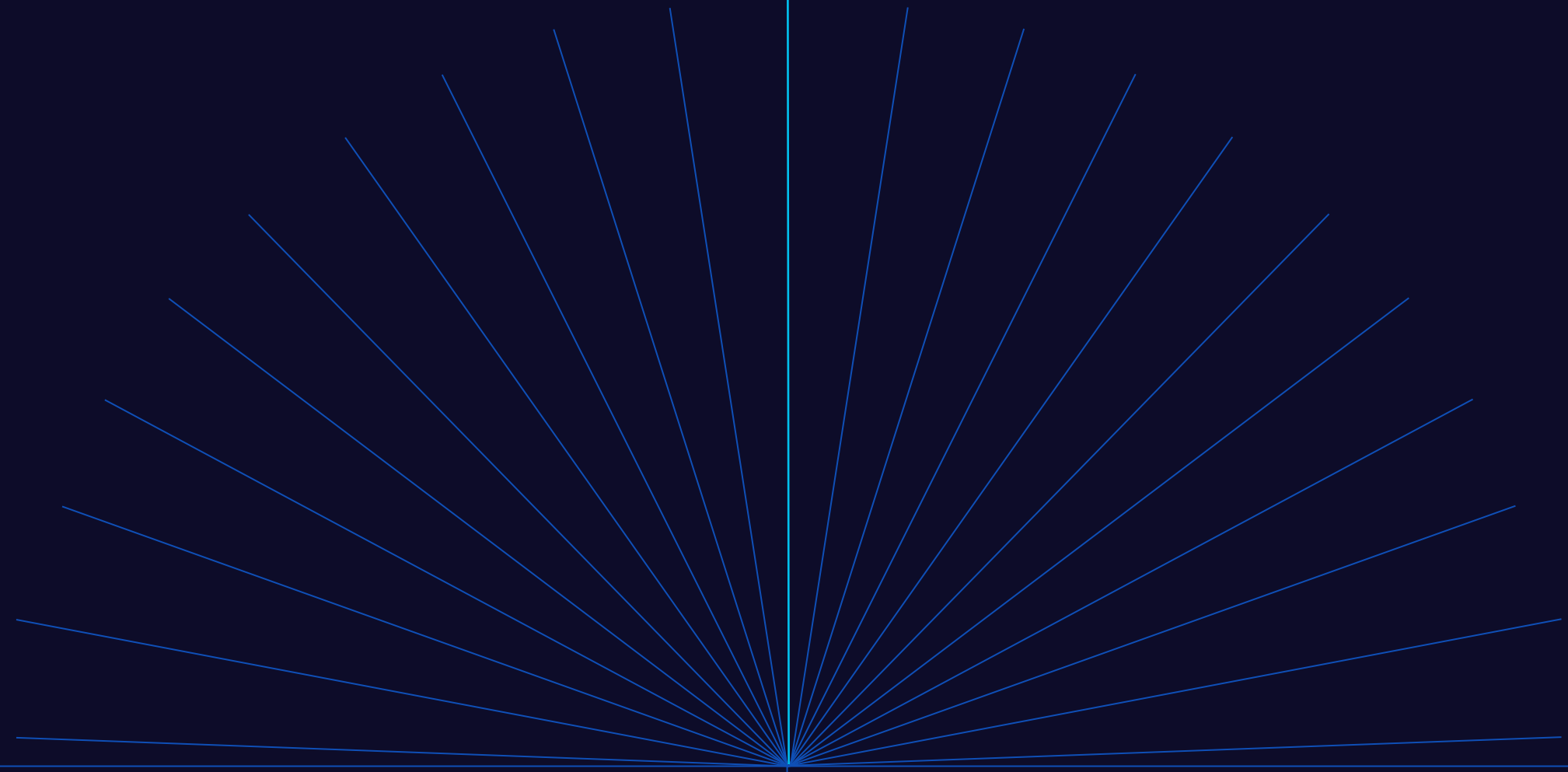

Sleuth

Sleuth Intel Hub

RNA Intelligence Report, 2026

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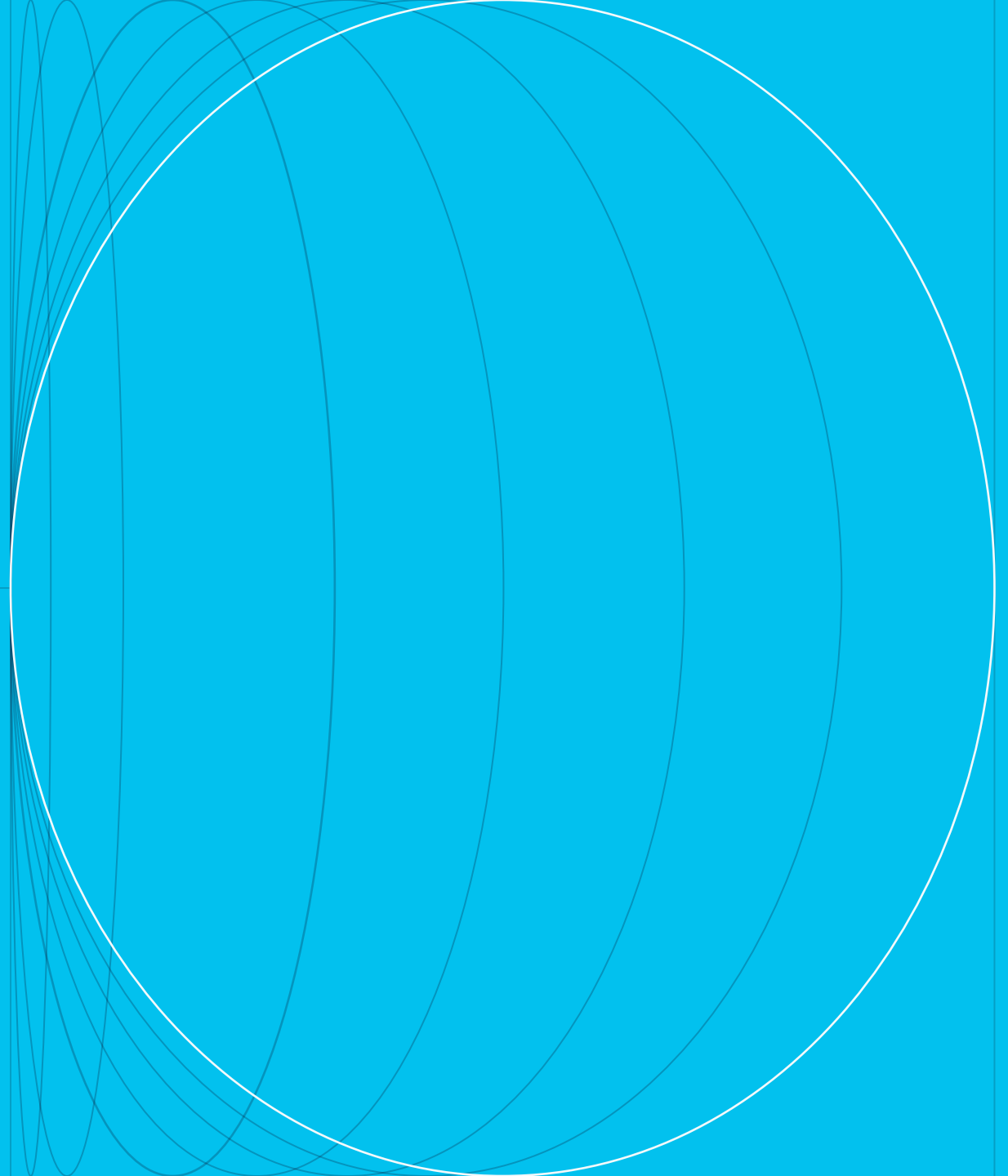
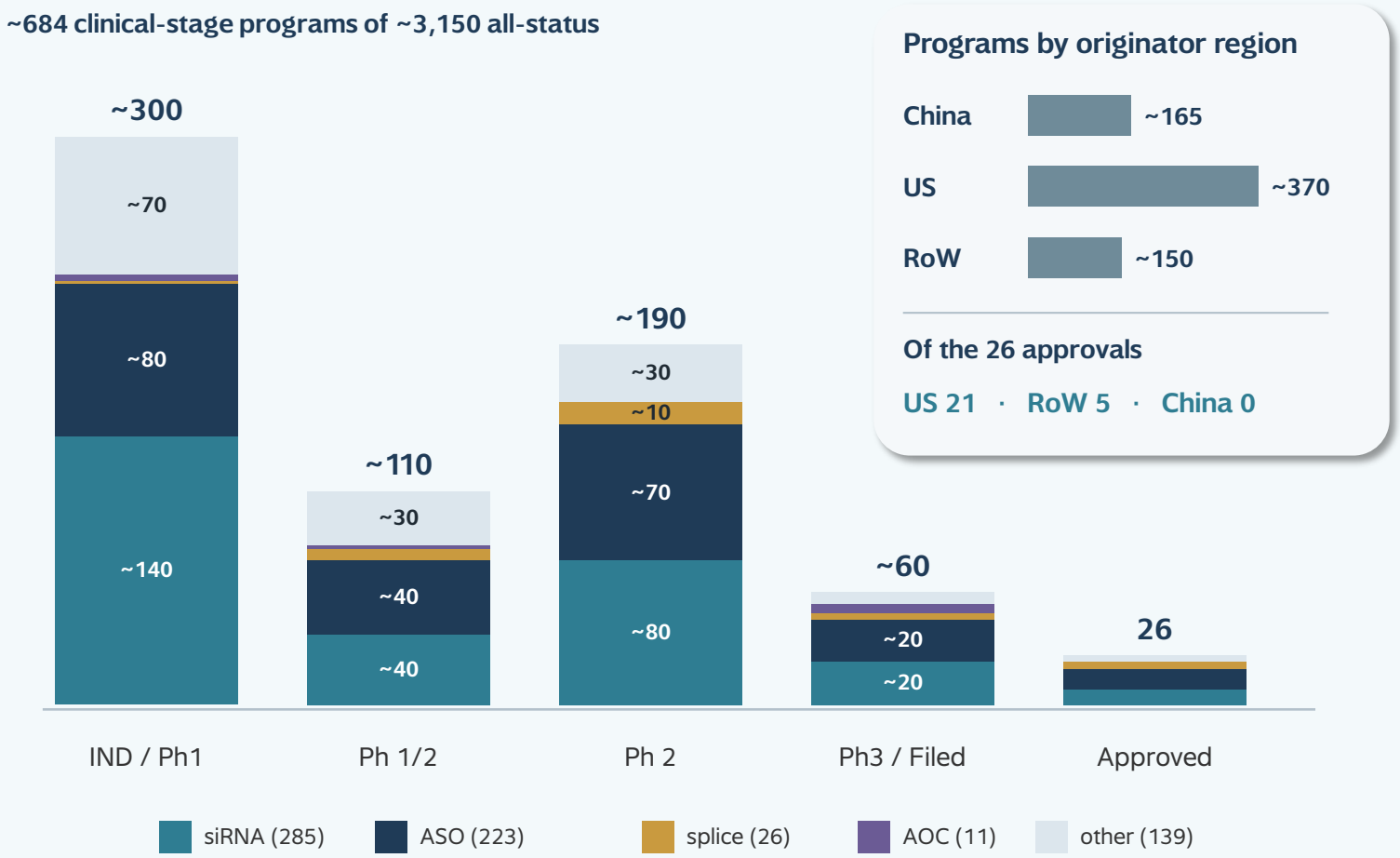
Section 1: The Data



Oligonucleotides are the only approved RNA therapeutic class outside of vaccines

ASO holds the most approvals (11 of 26) and siRNA the next 8, while siRNA still leads the pipeline by volume

Clinical pipeline by phase, chemistry, and company geographic origin[1]



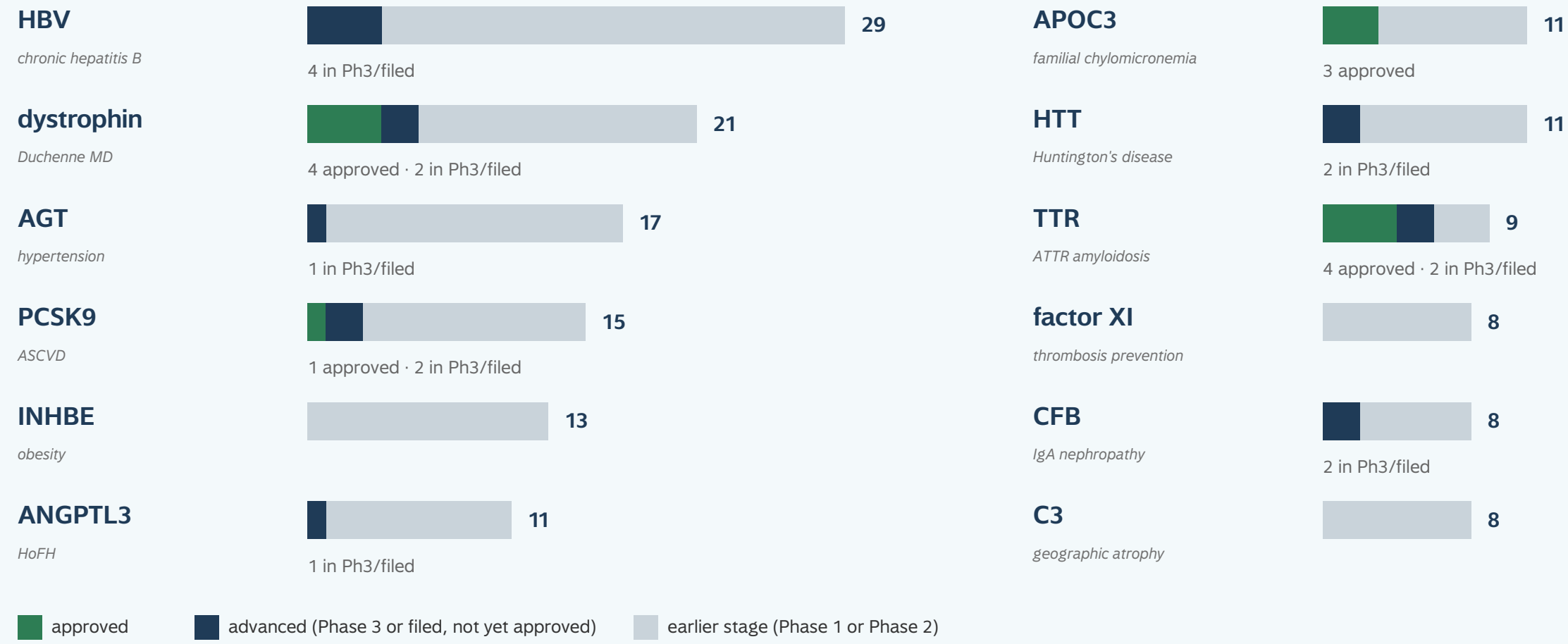
- Every approval sits in a chronic or rare-disease indication, where a durable oligonucleotide pays off most
- The chemistry mix shifts with stage: siRNA and ASO own the early IND and Phase 1 breadth, while splice and other chemistries hold a proportionally larger share of the late-stage programs.
- China has become a core contributor to the pipeline, though the West has been the originator for all approvals, with over ~80% from the US alone

[1] Therapeutic oligonucleotides only; prophylactic vaccines excluded.

Clinical programs concentrate on a few targets

Only a few targets are proven, so most new programs have begun to compete on delivery and dosing

Clinical programs per target, split by most-advanced stage



RNA targets by clinical program count and most-advanced phase, September 2026

siRNA dominates the cardiometabolic RNA field, crowding nine contested targets

84 active programs from 48 companies target just nine cardiometabolic pathways, and 77 of the 84 are siRNA

Target	Phase 1 & 1/2	Phase 2	Phase 3 / Reg.	Approved
AGT	ADARx, Arnatar Therapeutics, 华东医药 Huadong Medicine, Lepu Medical, RONA Therapeutics, Sunnovo	CSPC Innovent, 成都国为 Chengdu Gowell, Hengrui, Hitgen, Ionis, Novartis, 悦康药业集团	Roche	
INHBE	Alnylam, arrowhead pharmaceuticals, CMS 康哲药业, Hengrui, Hitgen, Innovent, Lepu Medical, RONA Therapeutics, SanegeneBio, Sirius Therapeutics, Vial	BaseCure Therapeutics, Wave Life Sciences		
PCSK9	Corsera Health, 君实生物 TopAlliance, RONA Therapeutics, SanegeneBio, Sirius Therapeutics, 悦康药业集团	RRGene	CSPC, 齐鲁制药 Qilu Pharmaceutical	Novartis
ApoC3	Alnylam, Fosun Pharma 复星医药, RONA Therapeutics, 中國生物製藥有限公司 Sino Biopharmaceutical Limited	Hengrui, Ionis, Ribolia Life Science		Ionis, arrowhead pharmaceuticals
ANGPTL3	君实生物 TopAlliance, Silence Therapeutics	Alnylam, Argo Biopharma, Lilly, CSPC, EDDING 亿腾, Lepu Medical	arrowhead pharmaceuticals	
Lp(a)	Salubris 信立泰, 悦康药业集团	CSPC, Hengrui, Novartis, Sirius Therapeutics	Amgen	
factor XI	ADARx, City Therapeutics, sirnaomics, 悦康药业集团	CRISPR Therapeutics, Ionis, Ribolia Life Science		
TTR	Argo Biopharma, Fangxiang			Alnylam, AstraZeneca, Ionis, sanofi
TMPRSS6	agios, BeBetter Med 必贝特, 華潤医药 CR Pharma	Silence Therapeutics	Ionis	

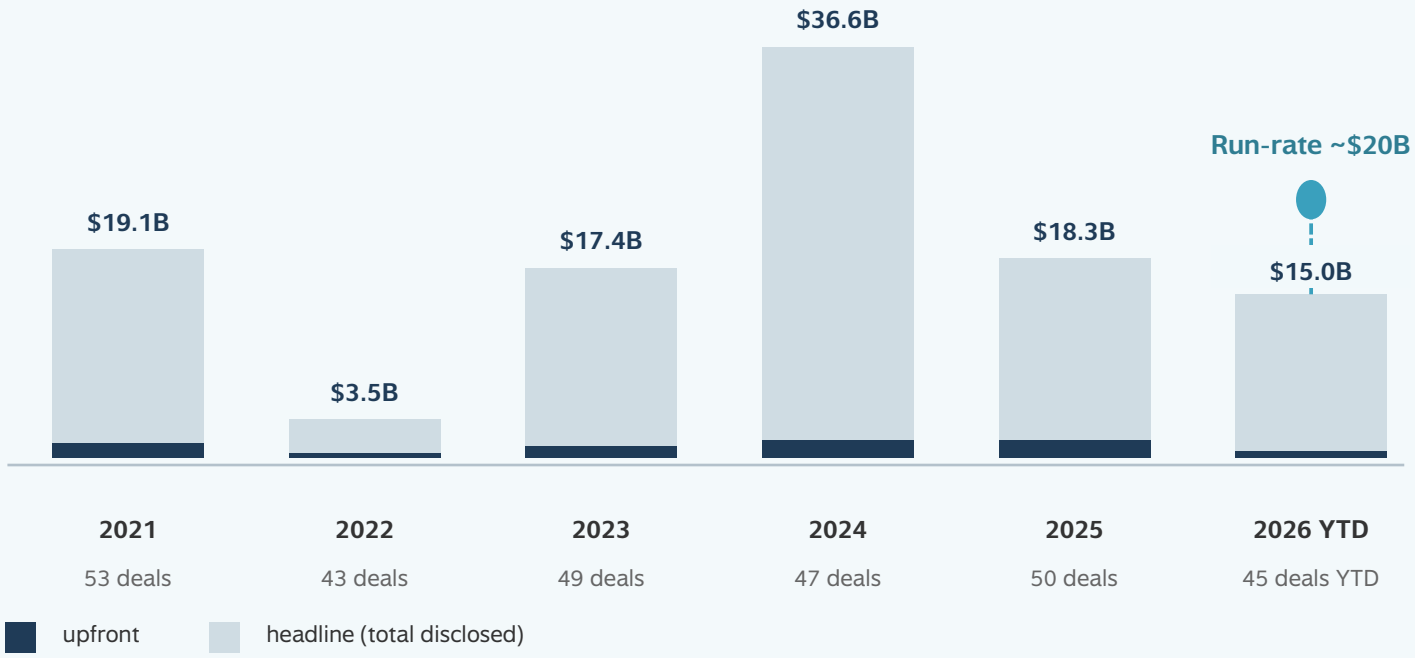
RNA competitive landscape, as of September 2026.

Dealmaking has remained high, though M&A has shifted to extrahepatic delivery

Licensing and collaboration value has run high since 2021, while M&A has concentrated with one buyer, Novartis

Marquee oligo M&A since 2023

Acquisition	Year	Headline value	What it buys
Novartis > Avidity	2025	**$12B**	Muscle antibody-oligo conjugates (DMD, DM1, FSHD)
Astellas > Iveric	2023	**$5.9B**	Eye aptamer (avacincaptad, geographic atrophy)
Novartis > Regulus	2025	**$1.7B**	Kidney conjugate (farabursen, ADPKD)
Novartis > DTx	2023	**$1.0B**	Neuro fatty-acid conjugates (FALCON platform)



- The M&A is mostly from a single-buyer: Novartis bought three extrahepatic delivery platforms across muscle, kidney and neuro from 2023 to 2025.
- Sarepta also locked up Arrowhead's extrahepatic delivery rights, with more platform deals expected to close ahead of the assets reaching clinical validation.
- Deals cluster in cardiovascular targets (AGT, PCSK9, ANGPTL3, ApoC3), and 2024's value jump was larger deals, not more of them.

Oligonucleotide deals, 2021 to September 2026

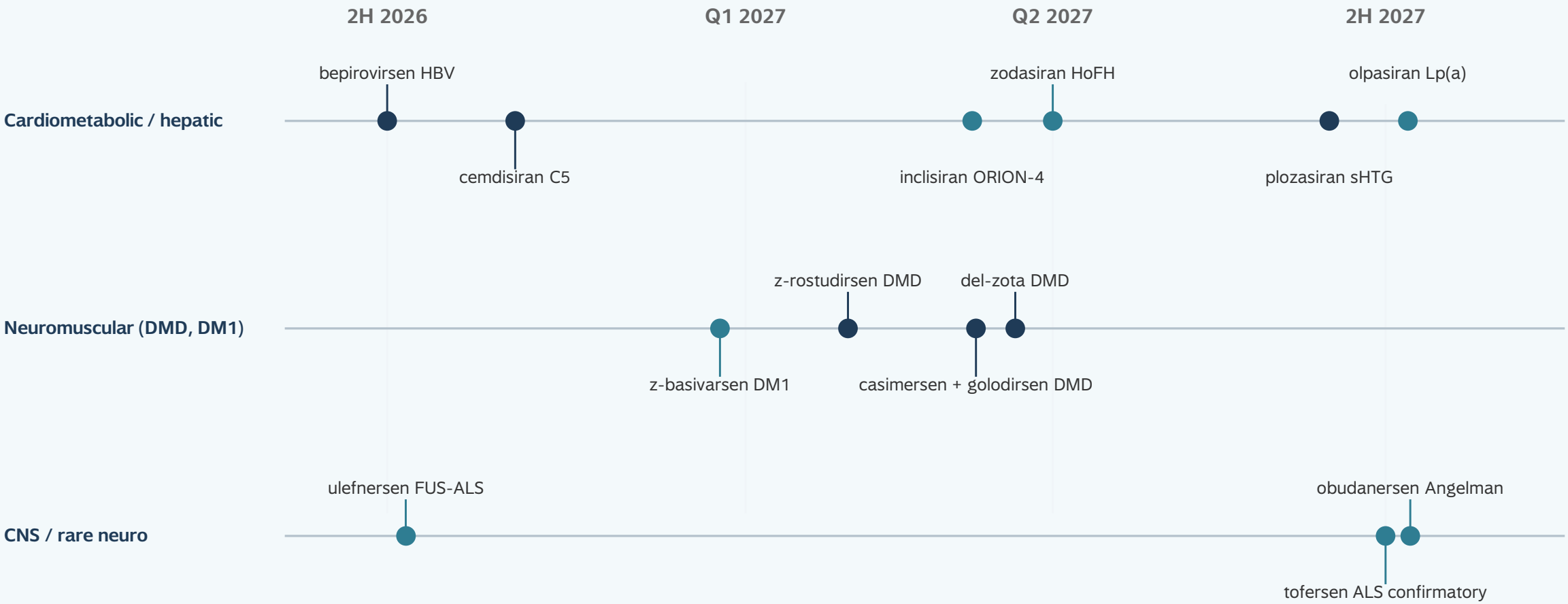
Near-term catalysts across TAs are mostly regulatory decisions on filed drugs

Most 2027 catalysts are approvals and filings, with additional efficacy readouts throughout

Select high-impact catalysts through end of 2027

regulatory decision data readout

NON-EXHAUSTIVE



Cardiovascular is proven as a TA focus for oligonucleotide, validated with 3 targets

Cardiovascular is the leading TA for oligonucleotides, delivered to the liver, with dosing from QM to Q6M

- Statins proved that lowering LDL cuts cardiovascular risk; PCSK9 was then validated as a target by genetics and anti-PCSK9 antibodies, and siRNA now competes on dosing durability.
- Top targets (PCSK9, APOC3, TTR) have proven clinical outcomes, while ANGPTL3 and Lp(a) have not yet reached clinical validation in cardiovascular indications.
- Lp(a) is the open question: pelacarsen lowered Lp(a) but missed its cardiovascular endpoint, so the class re-rates on the olpasiran readout.

Top targets among cardiometabolic programs

Increasing Clinical Validation

Target	Lead asset	Dosing	What the outcomes data shows
PCSK9	inclisiran	Q6M	PCSK9 lowering has proven cardiovascular benefit at class level; inclisiran's own outcomes trial (ORION-4) is still reading
APOC3	plozasiran	QM to Q3M	Approved in familial chylomicronemia; olezarsen approved alongside; broader cardiovascular outcomes still to read out
TTR	vutrisiran (+3)	Q3M	Four TTR drugs approved; HELIOS-B delivered a positive cardiovascular outcomes result in ATTR cardiomyopathy
ANGPTL3	zodasiran	Q3M	Phase 3 in HoFH and severe hypertriglyceridemia; lowers triglycerides, but no cardiovascular outcomes data yet
Lp(a)	pelacarsen	QM	Lp(a)HORIZON lowered Lp(a) sharply but missed its MACE cardiovascular endpoint, so knockdown is not yet proven on outcomes

Extrahepatic delivery is more proven locally, but is still early as a systemic option

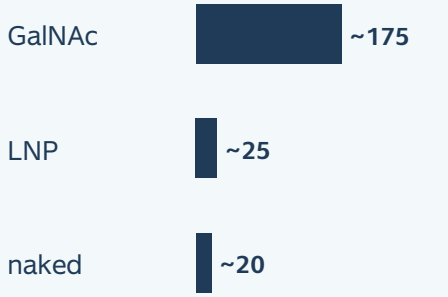
Most programs act outside the liver, but only a subset reach distant tissue, and each has a leading delivery tech.

Clinical programs by access tier and delivery technology

Liver
Easy, proven reach to liver cells

~235 programs[1]

Top delivery technologies (programs)



+15 programs in other techs

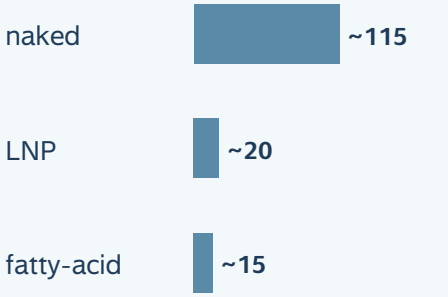
ROA: subcutaneous

Most advanced:
inclisiran (approved)

Local / Regional
Delivered on-site, skips the bloodstream

~200 programs[1]

Top delivery technologies (programs)



+55 programs in other techs

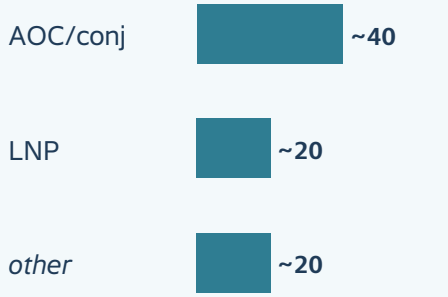
ROA: intrathecal / inhaled / eye

Most advanced:
nusinersen (approved)

Systemic Redirection
Bloodstream route to distant tissue

~80 programs[1]

Top delivery technologies (programs)



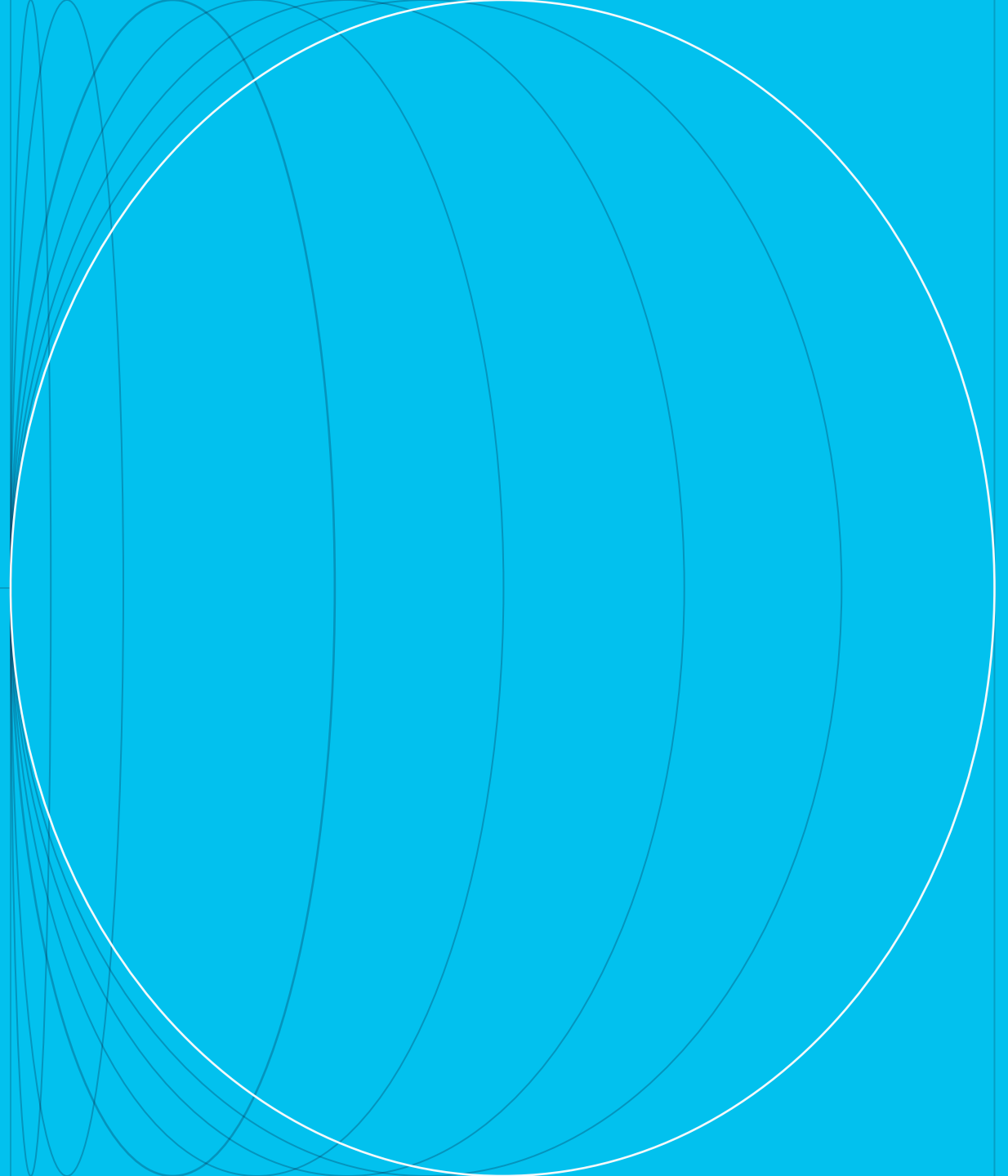
ROA: IV

Most advanced:
del-zota (filed)

- Many programs now are targeted extrahepatic, but a minority (~12%) reach a distant tissue through systemic redirection.
- Muscle leads with two AOCs filed (del-zota, z-rostudirsen), then kidney (Regulus, ADPKD), while CNS-systemic and tumor remain early.
- Each access tier has a premier delivery technology: GalNAc for the liver, naked chemistry for local-regional tissues, and conjugates for the systemic frontier.
- Local-regional is a known-route execution race with approved assets; while systemic redirection is earlier, and the winning delivery technology has yet to become clinically validated.

[1] ~25% of programs are unclassified. Clinical oligonucleotide programs by access model and delivery technology, September 2026. Systemic redirection = reaching a target beyond the liver or a proven local region.

Section 2: Sleuth Perspectives

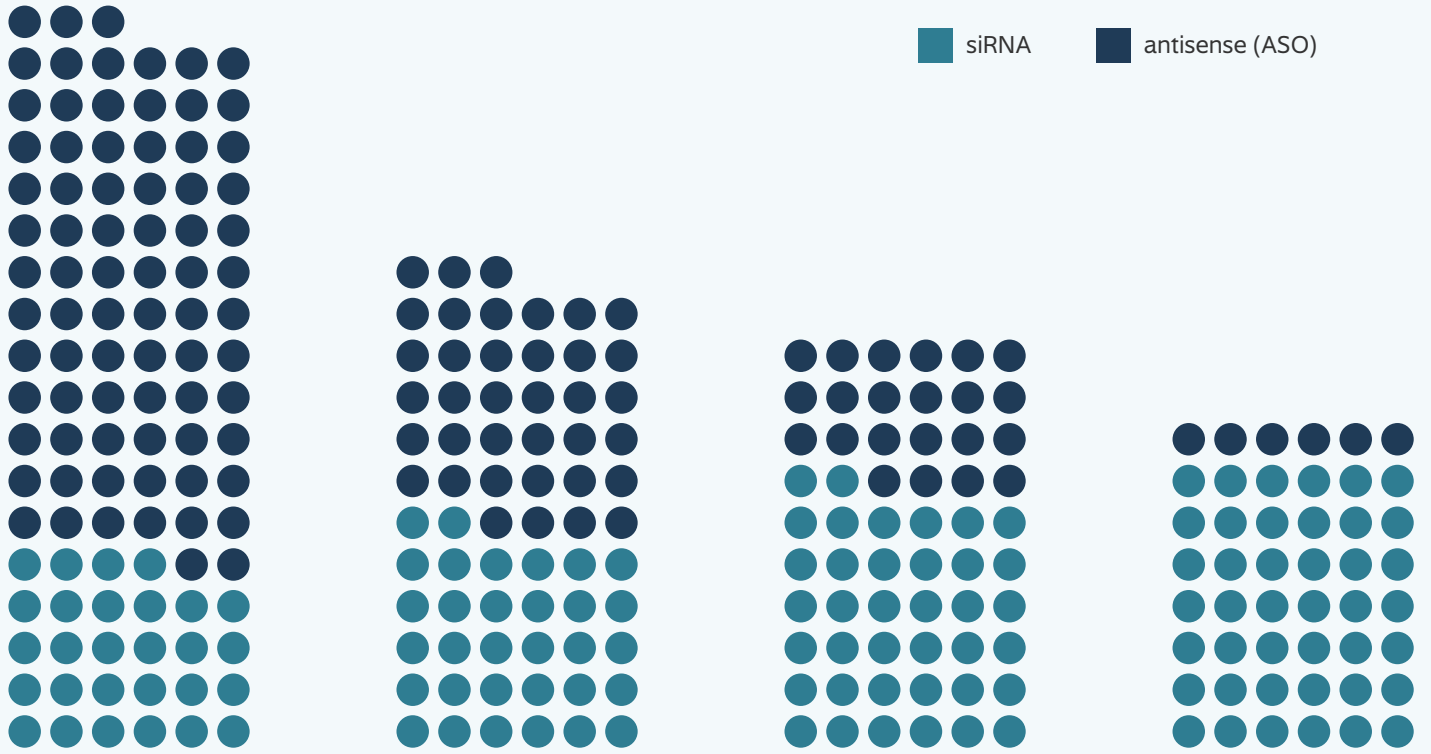


siRNA dosing is infrequent and that durability is the franchise edge

As dosing lengthens from weekly to twice-yearly, the siRNA asset volume increases

- siRNA is winning where adherence is the problem, as inclisiran (Leqvio) reached $1.2B in 2025 revenue with twice-yearly dosing.
- Across the 282 programs with a disclosed dosing interval, siRNA's share climbs as frequency decreases; most oligos are used chronically, so a longer dosing interval is a benefit when patients stay on a given therapy
- **Sleuth Insight:** Durability is a trade-off. siRNA buys adherence on chronic, well-validated liver targets, while ASO still leads where you need reach into CNS or muscle. Match the chemistry to whether the indication rewards convenience or demands access.

siRNA takes over as dosing gets less frequent and more durable

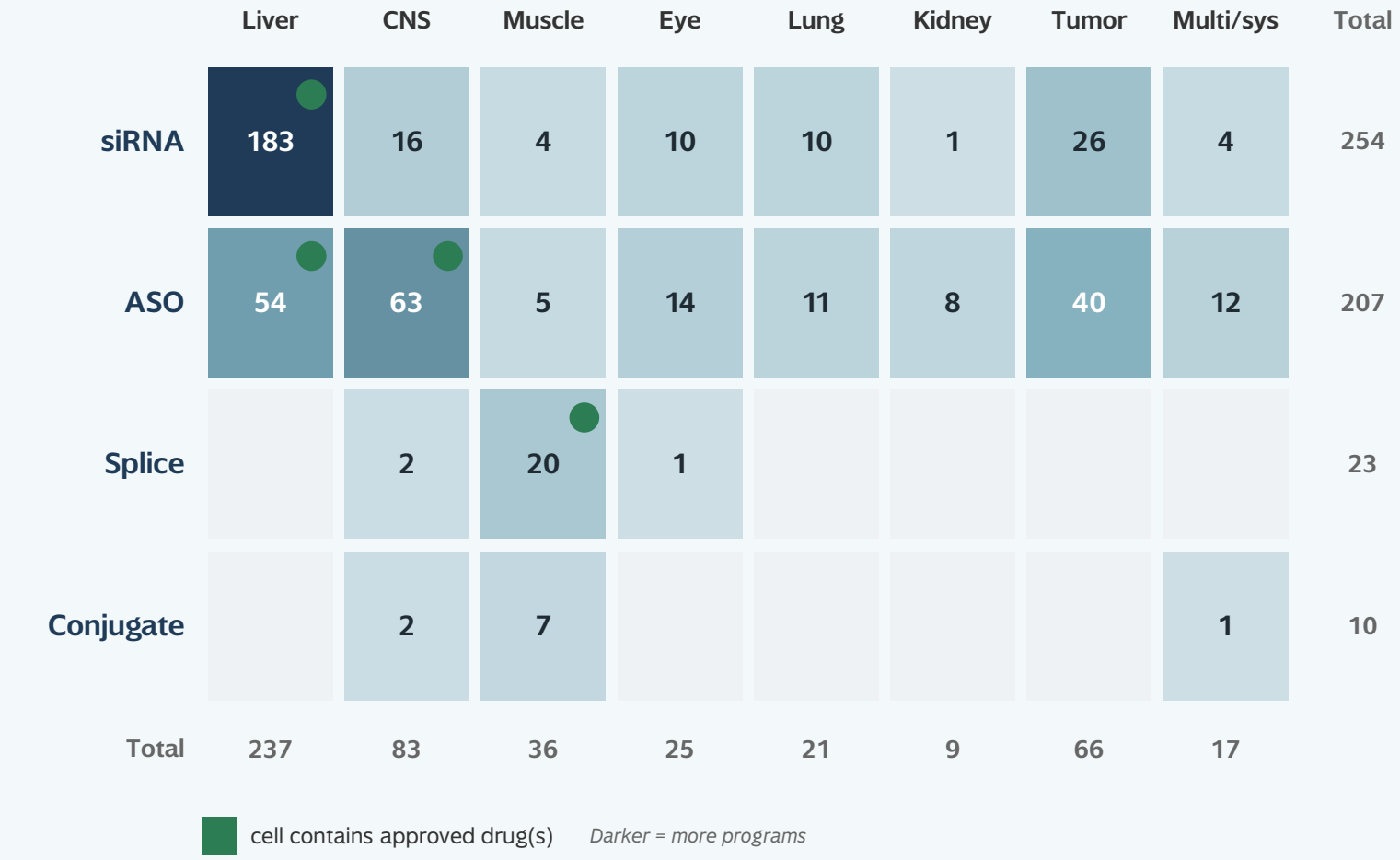


siRNA and ASO programs by dosing interval and chemistry, September 2026. Dosing interval is undisclosed for roughly a quarter of siRNA and ASO programs. Slide does not include splice, AOC, and other modalities.

Next-generation chemistries lead extrahepatic development

siRNA dominates the liver, pushing other chemistries to seek extrahepatic targets for commercial viability

Programs by chemistry and delivery tissue



- siRNA leads the liver in approvals, while ASO has liver development but a significant pipeline in CNS and tumor; splice has focused on muscle exon-skipping.
- Chemistries cluster by organ: GalNAc-siRNA fits hepatocyte uptake, intrathecal ASO reaches the CNS, and splice oligos fit exon biology of muscular dystrophy.
- **Sleuth Insight:** Tissue access is a chemistry decision, and reaching beyond the liver depends on the chemistry matched to the target (ASO for CNS, conjugates for muscle). The extrahepatic winners are likely to be decided by the fit of chemistry rather than raw program volume.

Programs by chemistry and delivery tissue, September 2026. ~51 programs not included across less developed organs / tissues.

Multiple late-stage oligo programs missed their clinical endpoints in 2026

The 2026 misses diverge by whether the target is proven and if a rival oligo already works in the space

- Five key late-stage programs missed their clinical endpoints in 2026, across Lp(a), DM1, Angelman, TTR-CV and Huntington's.
- With rival oligos already approved on one target (TTR) and still advancing on another (Angelman), the misses reprice specific assets and two target hypotheses.
- **Sleuth Insight:** Genetic causality is established across these targets, but whether lowering them changes outcomes is unproven. Lp(a) and HTT classes still need outcomes validation. TTR has proof, so a miss reprices the asset. On Angelman and DM1, the biology is causal but the clinical endpoint has not yet followed.

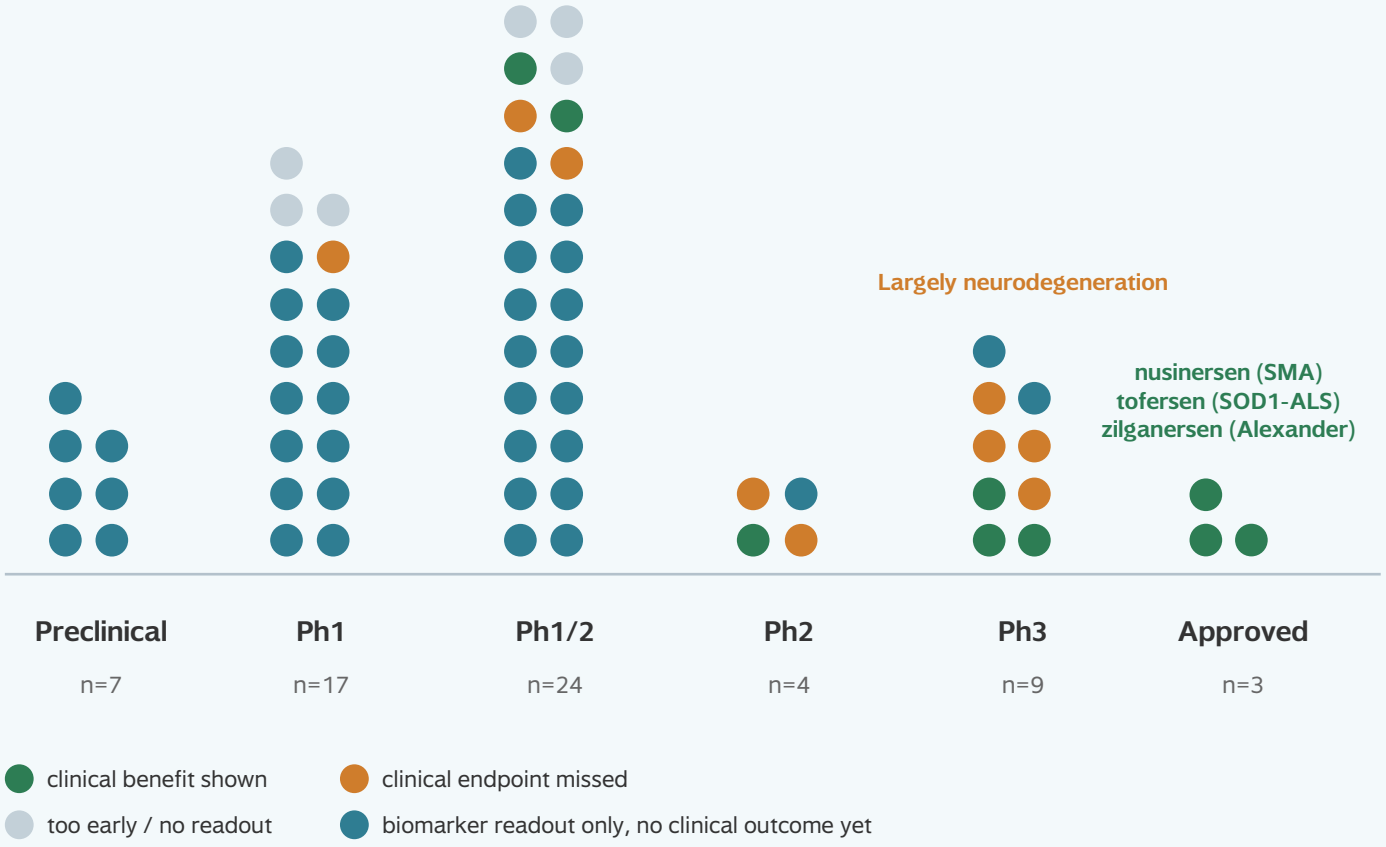
Late-stage programs that hit their molecular target but missed the clinical endpoint

Asset	Target	Trial	What happened in 2026
pelacarsen *clinical translation unproven*	Lp(a)	Lp(a)HORIZON	Lp(a) was lowered sharply, but the trial missed its MACE cardiovascular primary, so Lp(a) lowering is not yet proven on outcomes.
del-desiran *endpoint*	DM1	HARBOR	Splicing biomarkers moved, but HARBOR missed the vHOT functional primary in myotonic dystrophy, and the program is under review.
GTX-102 *endpoint*	Angelman	Aspire	Target engagement was clean, but Aspire missed the Bayley-4 cognitive endpoint, so the molecular hit did not translate to function.
eplontersen *asset / trial*	TTR CV	CARDIO-TTRansform	TTR was lowered, but the trial missed its cardiovascular primary overall; only a monotherapy subgroup read nominally positive.
tominersen *clinical translation unproven*	HTT	GENERATION HD2	mHTT was lowered, but there was no clinical benefit at 16 months in Huntington's disease, and Roche discontinued the program.

Approved CNS oligonucleotides are all intrathecal rare-disease drugs

Three intrathecal ASOs are approved in rare genetic disease, while the large neurodegeneration targets failed

Intrathecal ASOs across clinical development stages



- The three approved CNS oligos all use intrathecal delivery in single-gene disease, proving the CNS playbook locally, while systemic remains pre-validation.
- The most difficult CNS targets (HTT, tau, Angelman) keep missing on clinical function, while systemic CNS delivery is still only four programs.
- **Sleuth Insight:** CNS splits into two risk classes. It is proven with intrathecal delivery in monogenic disease (SMA, SOD1-ALS, Alexander disease), and unproven at frontier of neurodegeneration and systemic reach.

CNS oligonucleotide field, n=64, September 2026; across trials, not head-to-head

Muscle conjugates hit on delivery, but proving clinical function is the harder test

The delivery platform is validated, but not function: two AOCs are filed while a lead conjugate missed its endpoint

The muscle-conjugate field (30+ programs) by stage and latest readout

Asset	Indication	Chemistry	Stage	Readout Context	Verdict
del-zota	DMD exon 44	AOC	Filed / BLA	BLA accepted with Priority Review; systemic muscle delivery and the regulatory path is engaged, clinical function is still to read	**Filed (BLA accepted)**
z-rostudirsen	DMD exon 51	AOC	Filed	DELIVER restored 5.46% dystrophin; PDUFA decision set for January 2027	**Filed (PDUFA Jan 2027)**
del-desiran	DM1	AOC	Phase 3	HARBOR missed its vHOT functional primary in myotonic dystrophy; the program is under review	**Endpoint missed**
z-basivarsen	DM1	AOC	Phase 3	Phase 3 HARMONIA initiated 2026; the near-term registrational readout comes from the ACHIEVE cohort, expected 2027	**Awaiting readout**
del-brax	FSHD	AOC	Phase 1/2	FORTITUDE hit the DUX4 biomarker, but there is no functional or clinical readout yet	**Biomarker; function pending**
exon-skippers *(4 of 9 approved)*	DMD	PMO / peptide	Approved	Four exon-skippers are approved on dystrophin production; the ESSENCE confirmatory study of casimersen and golodirsen missed its functional endpoint	**Approved; function unconfirmed**

Sleuth Insight: The bottleneck for muscle conjugates has moved from delivery to clinical function. del-zota validated the delivery, but del-desiran shows function is not guaranteed, and the delivery platform is what holds the value, as Novartis' roughly $12B Avidity deal shows.

Muscle conjugate field, n=30+, September 2026; across trials, not head-to-head

Sleuth predictions

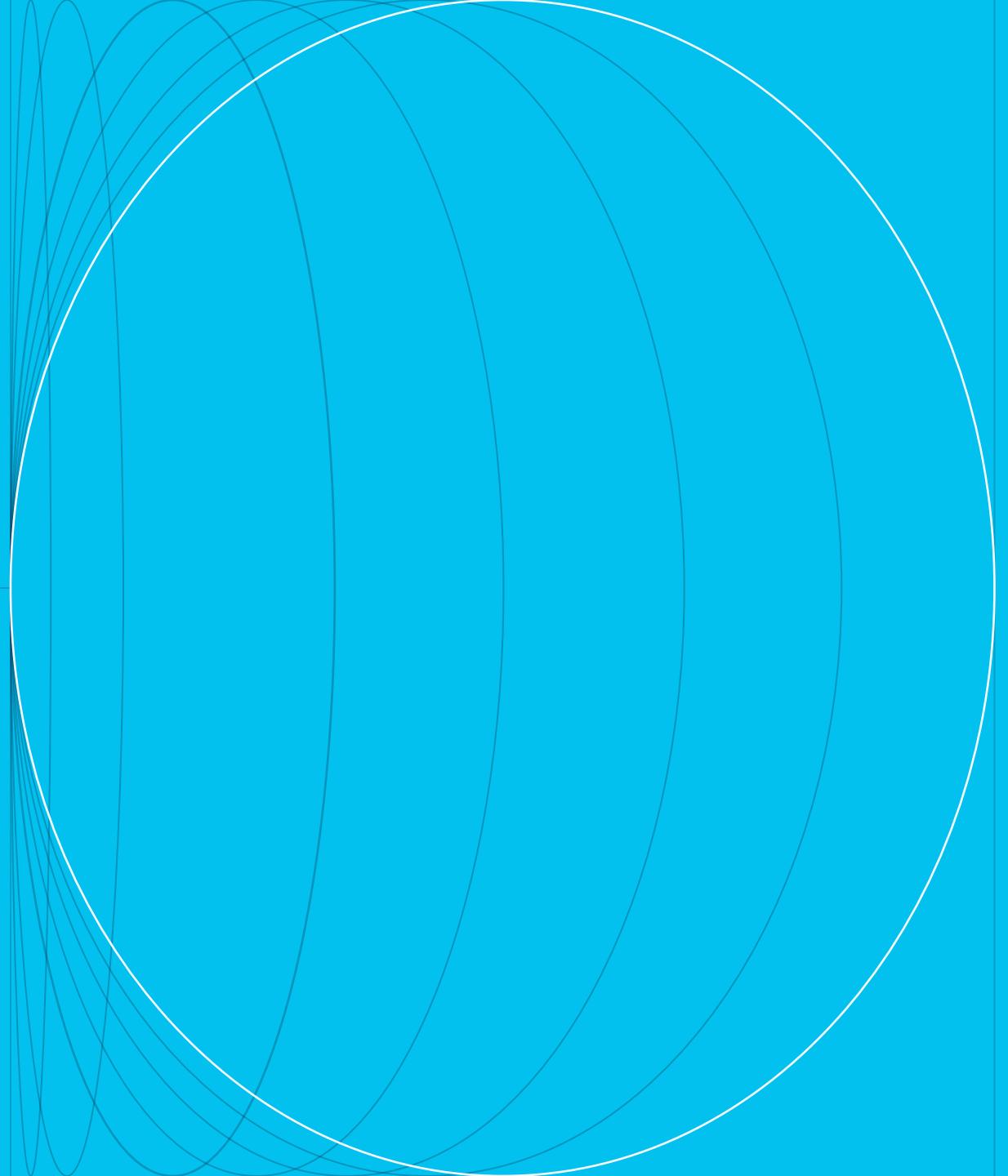
Our read when we look beyond the data

1. **The first systemic extrahepatic oligo approval lands in 2027 and resets the field:** With del-zota filed and z-rostudirsen at a Jan 2027 PDUFA, a muscle conjugate becomes the first oligo delivered systemically to a tissue beyond the liver, since CNS and eye oligos are delivered locally, shifting deal and pipeline focus to the next tissue.

2. **A delivery-platform deal exceed $2B before pivotal proof:** Novartis rolling up Avidity, Regulus, and DTx shows buyers are pricing the delivery platform and paying up well before the pivotal readout. Expect at least one more delivery-platform acquisition or major licensing deal in the $2 – 3B range to close ahead of clinical proof.

3. **The Lp(a) class still needs the target to be validated:** Pelacarsen lowered Lp(a) sharply but missed on MACE, so olpasiran (Amgen) and lepodisiran (Lilly) are testing whether lowering Lp(a) helps at all. If they miss, a multi-billion-dollar thesis collapses across the class; if they hit, durable siRNAs will likely take the market over ASOs.

How Sleuth can help



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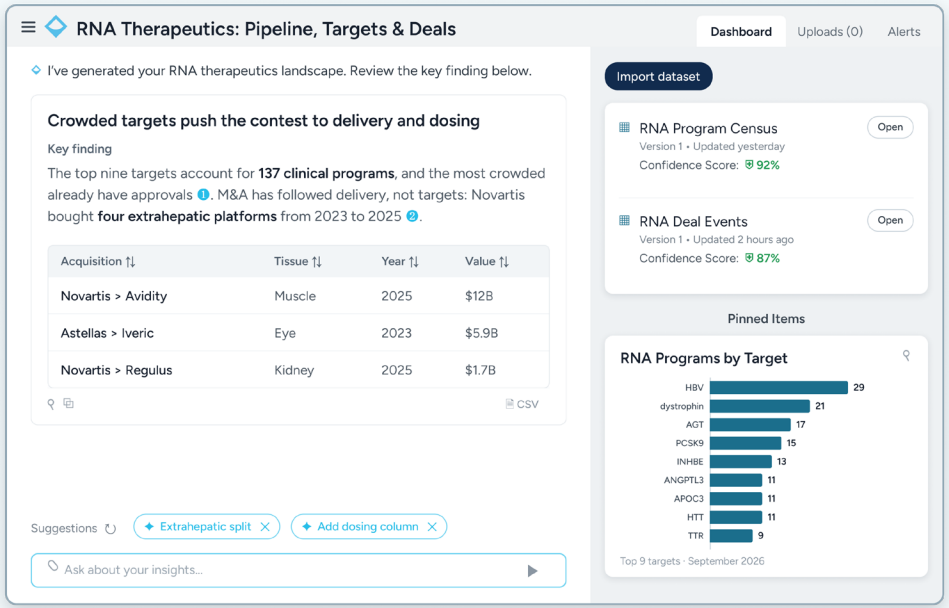
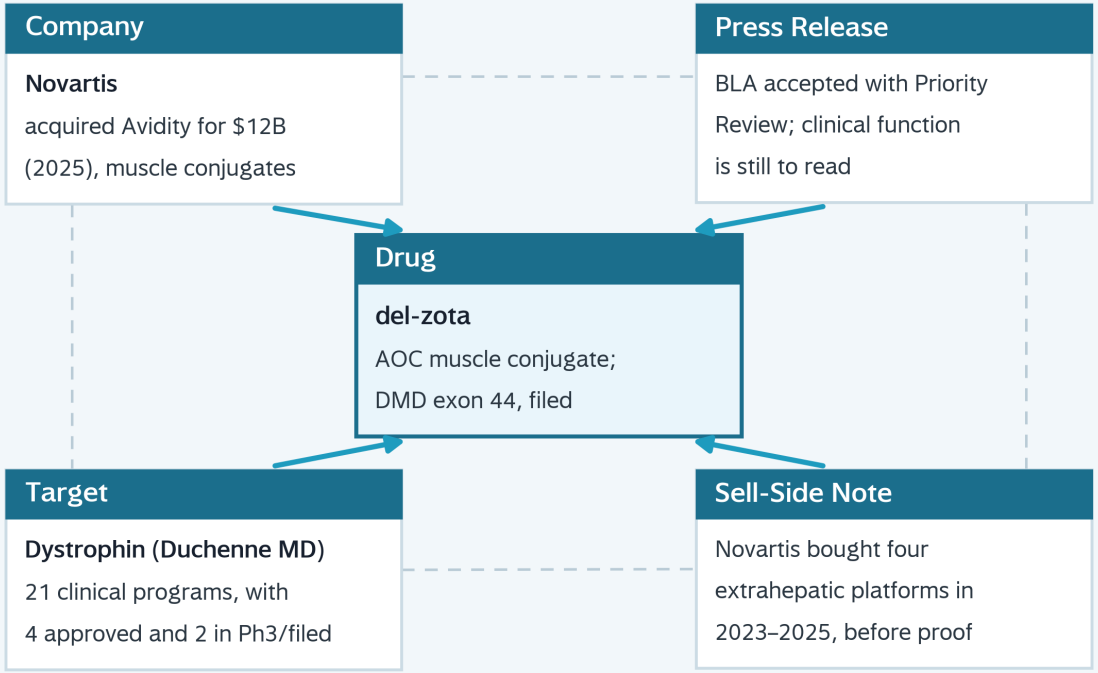
Main Takeaway: RNA is proven in the liver on a few crowded targets. Extrahepatic delivery is the next franchise, and the first verdicts land in 2027.



Intelligence you can stand behind

Bring Sleuth your questions, and pre-connected intelligence surfaces automatically. Our knowledge graph connects data across the landscape, with full traceability.

Illustrative knowledge graph for del-zota (DMD exon 44)



Every claim traceable to source document

Case study: Epana Bio indication prioritization

What happens when you evaluate 167 indications with the same effort as six? Read the full case here.

Stakes: Epana Bio needed to make a high-stakes decision on which indications to pursue first for their targeted cell depletion therapeutics.

Challenge: Standard evaluation is often limited by bandwidth, forcing teams to choose from just a few familiar diseases.

Approach: Epana ran a comprehensive evaluation of 167 indications, using an iterative framework to challenge scores and pressure-test every assumption.

Outcome: Leadership built the conviction needed to select lead indications and raise capital with an investor-ready narrative.

167	Indications evaluated
25	Evaluated with a tailored Epana focus that most processes never reach
4	Shortlisted for deep commercial diligence
1	Optimized basket

"All the strategy that used to be proprietary to pharma — the 'game within the game' that actually drives strategic decisions — Sleuth made that accessible to a nine-person biotech. **I think it's the most disruptive, amazing thing for small organizations like ours.** A massive, massive unlock."

Danny Wells, PhD
CEO, Epana Bio