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Biotech catalysts on the horizon

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The second quarter should bring pivotal data for Karuna and key cardiomyopathy results for Alnylam, while Ionis's eplontersen lags in amyloidosis.

An earlier analysis by *Evaluate Vantage* concentrated on upcoming big pharma data reveals; here, we look at the clinical results due for biotech companies with a market cap of $1bn and above.

Pivotal data are expected on Karuna's schizophrenia project KarXT, and the hope is that it can maintain the effect size seen in an earlier study. Alnylam, meanwhile, is keen to expand Onpattro into cardiomyopathy in amyloidosis. Ionis might be lagging behind with its amyloidosis project eplontersen, with polyneuropathy results due soon, but it has at least secured a big pharma partner.

Karuna Emerges

KarXT is **Karuna**'s lead programme. It is a fixed-dose combination of xanomeline, a muscarinic M1/M4 agonist, and trospium chloride, a muscarinic antagonist, an approach designed to reduce peripheral side effects. The therapy performed well in an earlier study, but a phase 3 study will show whether the effect size narrows – a common issue for CNS studies.

In the phase 3 Emergent-2 trial, 246 patients were given KarXT twice daily versus placebo. The primary endpoint, the change from baseline in positive and negative syndrome scale (PANSS) total score at week 5, is the same as in the phase 2 Emergent-1 trial.

Emergent-1, which enrolled 182 patients, showed a statistically significant placebo-adjusted 11.6-point mean reduction in total PANSS score at week 5. Between treatment and placebo there were also similar rates of weight gain and somnolence, issues that have plagued older schizophrenia drugs.

For filing the FDA says Emergent-1 plus a successful phase 3 and additional safety data are needed. A second pivotal study, Emergent-3, is ongoing and data were due in the second half of this year; however, more than half of the trial sites are in Ukraine, leading Karuna to withdraw its previous timing guidance.

Despite the setback Karuna should have enough data for a filling as Emergent-5, an ongoing open-label study, is to be upsized and should provide long-term safety and tolerability data.

Amyloidosis

Apollo-B data will see whether **Alnylam** can move **Onpattro**, its intravenous RNAi therapy, into cardiomyopathy of transthyretin-mediated amyloidosis. Onpattro is already approved for polyneuropathy, a

disorder where amyloid is deposited in the peripheral nerves, but getting a win in cardiomyopathy would open a bigger market.

The primary endpoint of Apollo-B is the change from baseline in six-minute walk test at 12 months. Sentiment over the endpoint took a hit at the end of last year when Bridgebio's acoramidis failed on the same measure, with placebo patients performing better than expected.

There are several theories regarding Bridgebio's failure, including a possible training effect on six-minute walk, and that the study recruited patients with mild disease. Alnylam has said it has minimised the number of screening and baseline assessments to try and combat a potential training effect.

Results from Apollo-B will read through to Alnylam's subcutaneous Onpattro follow-on, vutrisiran. This project has a Pdufa date in April for polyneuropathy, and an ongoing cardiomyopathy study, Helios-B, is expected to yield data in 2024.

Another company hoping to make its mark in a crowded amyloidosis space is **Ionis**. Data on its subcutaneous antisense project **eplontersen** are due in polyneuropathy. The group struck a partnership in December with **Astrazeneca** worth $200m up front.

Eplontersen's own cardiomyopathy data are still a long way off as its Cardio-TTRansform study has a primary completion date in 2024. Here the primary measure is a composite outcome of cardiovascular mortality and CV events, with the six-minute walk test as a secondary.

The table below contains a fuller list of upcoming catalysts with consensus forecasts from *Evaluate Pharma.*

Clinical catalysts in Q2 2022 (excludes Covid-19 data), market cap $1bn+

Project	**Company**	**Setting**	**Q2 clinical catalyst**	**2026e indication sales ($m)**	**Note/*Vantage* coverage**
Cabometyx + Opdivo + Yervoy	Exelixis/ Ipsen/ Takeda	1L renal cancer	Ph3 Cosmic-313	1,962*	Label expansion (*Liver cancer loss piles the pressure on Exelixis*)
Zuranolone (Sage-217)	Sage/ Biogen/ Shionogi	Postpartum depression	Ph3 Skylark mid year	1,620 (SBI not split out)	Complete rolling NDA submission in major depressive disorder H2, with PPD filing expected in 2023
Repotrectinib	Turning Point	NSCLC	Topline blinded independent central review data from TKI-naive Ros1+ NSCLC Trident-1 due 2Q	1,026	ORR data on track for Q2, but full durability data may not be fully mature (*Triple meeting – early data give and they take away*)
KarXT	Karuna	Schizophrenia	Ph3 Emergent-2 mid year	988	See text
Onpattro	Alnylam	ATTR amyloidosis with cardiomyopathy (wild-type & hereditary)	Ph3 Apollo-B topline mid year	765 (approved for polyneuropathy)	See text
		Indolent systemic	Ph2 Pioneer registration-		Label expanding, Blueprint believes that a 30% delta vs placebo in total symptoms

Clinical catalysts in Q2 2022 (excludes Covid-19 data), market cap $1bn+					
Ayvakit	Blueprint	mastocytosis	enabling Part 2	652*	improvement at 24 wks would represent a clinically meaningful result (Leerink)
GTX-102	Ultragenyx	Angelman syndrome	Ph1/2 cohorts 4 and 5 in Canada/UK	344	Antisense, previously paused due to safety issue
EDP-938	Enanta	RSV (adult)	Ph2 topline	323	N-protein inhibitor, expecting lots of RSV vaccine data this year from Pfizer/Glaxo/J&J
Vyvgart (intravenous)	Argenx	Immune thrombocytopenic purpura	Ph3 Advance	305	Approved in myasthenia gravis and subQ expected to be filed by YE (*Argenx takes a step towards convenience*)
Translarna	PTC Therapeutics	Duchenne muscular dystrophy caused by nonsense mutations	Ph3 Study 041	261	Been turned down by the FDA three times already, refiling expected pending Study 041 data
Eplontersen	Ionis/ Astrazeneca	Hereditary ATTR amyloidosis polyneuropathy	Ph3 Neuro-TTRansform interim analysis mid year	260 (under amyloidosis)	See text
CTX110	Crispr	B cell malignancies	Ph1 Carbon, additional data	243	Anti-CD19 Car-T, concerns over a lack of durability (*Crispr's reminder about allogeneic Car-T redosing*)
CTX120	Crispr	Multiple myeloma	Ph1 topline H1	135	Anti-BCMA Car-T
Troriluzole	Biohaven	Spinocerebellar ataxia	Ph3 Study 206 H1	95	*Biohaven's high-risk bet*
PN-943	Protagonist	Ulcerative colitis	Ph2 Ideal	87	α4β7 integrin antagonist (*Protagonist will need more than perseverance to play in bowel disease*)
Low-dose Truseltiq (infigratinib)	Bridgebio	Achondroplasia in children aged 3-11	Ph2 Propel 2 mid year	71	FGFR1-3 inhibitor, approved for 2L cholangiocarcinoma (Biomarin's Voxzogo is approved in patients aged ≥5, but data disappointed in younger patients)

Clinical catalysts in Q2 2022 (excludes Covid-19 data), market cap $1bn+					
CTX130	Crispr	Solid tumours and haematologic malignancies	Ph1 topline Cobalt-Lym, Cobalt-RCC H1	41	Anti-CD70 Car-T
Bempegaldesleukin +/- Opdivo/Keytruda	Nektar/Bristol	1L RCC, 1L urothelial cancer	Ph3 in 1L RCC + Opdivo vs TKI, Ph2 Pivot-10 in 1L cisplatin-ineligible urothelial cancer + Opdivo	–	Failed in melanoma and NSCLC (*Time for Nektar to Pivot*)
Nirogacestat	Springworks	Desmoid tumours	Ph3 DeFi	–	*Springworks seeks cancer win as a prelude to something bigger*

**Already on the market in different treatment line. Source: clinicaltrials.gov, Evaluate Pharma & company releases.*