Evaluate Vantage

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Biotech’s near-term key catalysts

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Important data reveals are expected from Madrigal, Arrowhead and Ascendis, with details from Biogen and Eisai due at a conference.

After sifting through big pharma's data reveals for the rest of 2022, *Evaluate Vantage* takes a look at the clinical results expected for biotech companies with a market cap of $1bn and above.

As with big pharma, Alzheimer's data represent the key event of the period. Biogen and Eisai have already toplined a positive result with lecanemab in early Alzheimer's, and detailed data are due at the CTAD conference in November. Apart from this, pivotal data from Madrigal could support an accelerated filing for resmetirom in Nash, while Arrowhead and Takeda’s RNAi project fazirsiran will yield results from its first placebo-controlled test in a rare liver condition. Ascendis, meanwhile, hopes to outshine Biomarin in young patients with achondroplasia.

Nash clash

If a pivotal trial of **Madrigal**’s thyroid hormone receptor-β agonist **resmetirom** succeeds, it will form part of a filing in Nash – a disease that has so far seen huge investment from biopharma for little reward.

The Maestro-Nash study enrolled biopsy-confirmed F2/F3 patients and tested two doses of resmetirom, 80mg or 100mg, against placebo. Results are expected from the first 900 patients that have progressed through 52 weeks of treatment.

The study’s dual primary surrogate endpoints will be confirmed by biopsy, and only one of the endpoints needs to be met for the study to be classed a success. The measures are Nash resolution with no worsening of fibrosis, or a one-point decrease in fibrosis with no worsening of Nash. A key secondary endpoint is lowering of LDL-C.

Madrigal has said it will use two independent pathologists to evaluate all liver biopsy slides, in addition to AI and machine learning to read images as an exploratory analysis.

Both Madrigal’s Maestro-Nash and another study called Maestro-NAFLD-1, in patients with presumed Nash, will be used for an accelerated filing in the US. The NAFLD-1 study met its safety primary endpoint, and has shown reductions in liver fat content by MRI-PDFF and Fibroscan. There were positive trends on fibrosis, as measured by Fibroscan, but these were not statistically significant.

Madrigal’s main competitor, Intercept, recently reanalysed biopsy data from its Regenerate study using three pathologists, after originally using just one. The study, testing Ocaliva, again met one of its co-primary

endpoints, fibrosis improvement, but only at the higher dose. Toxicity, in particular pruritus, continues to be a problem.

Ocaliva received a complete response letter from the FDA in 2020 and data from a phase 3 study in more advanced Nash patients are due in the fourth quarter.

Mutant protein

Another condition that can manifest in the liver is alpha-1 antitrypsin deficiency, a genetic disorder characterised by the build-up of mutant AAT protein (Z-AAT). This causes progressive damage and in rare cases patients require a liver transplant.

Arrowhead and its partner **Takeda** are developing an RNAi project designed to reduce the hepatic production of Z-AAT. The phase 2 Sequoia study enrolled 42 patients and tested three different doses of ARO-AAT, also known as **fazirsiran**, versus placebo.

The primary measure is the change from baseline in serum Z-AAT at week 16. An open-label phase 2 study showed a median reduction of Z-AAT in the liver of 83% over two cohorts of 16 patients in total, measured at 24 or 48 weeks. There were also signals of improving liver function and fibrosis.

A pivotal phase 3 trial of fazisiran is on track to start in the coming months. The main RNAi competitors for Arrowhead are Alnylam and its partner Novo Nordisk, the latter through its acquisition of Dicerna. Those groups are developing belcesiran, also called NN6021, which showed a mean reduction in Z-AAT of 77% after a single 6mg/kg dose in phase 1; analysts note that repeat dosing could deepen the knockdown. The phase 2 Estrella study is recruiting.

Accomplished?

Data are due with **Ascendis's Transcon CNP** in young children with achondroplasia, and the project needs to outshine competitors in this patient group. Biomarin's Voxzogo gained accelerated FDA approval last year in children aged 5 and over, but results in younger children disappointed.

The upcoming Accomplish study tests five different doses of Transcon CNP versus placebo. There are 60 enrolees aged between two and 10, with about 40% 2-5 years old. The primary endpoints are safety and annualised height velocity at one year.

Evercore ISI analysts note that the younger age group should experience the most improvements since they are growing rapidly and have larger deficits versus normal stature. Ascendis plans to start a phase 2b in children down to two years of age. Biomarin has early studies in children under two, but these will not report until 2026.

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

Big biotech's Q4 clinical catalysts					
Product	**Company**	**Therapy area**	**Catalyst**	**2028e indication sales ($m)**	**Note/Vantage coverage**
Lecanemab (BAN2401)	Eisai/Biogen	Early Alzheimer's disease	Ph 3 Clarity AD confirmatory study, detailed data at CTAD November 29	1,451	Released topline data at the end of September, also expecting data from Roche with gantenerumab, see big pharma story
Resmetirom	Madrigal	Biopsy confirmed Nash	Ph3 topline Maestro-Nash biopsy study	1,061	See text
Zimberelimab +/- domvanalimab +/- etrumadenant	Gilead/Arcus	1L PD-L1 50%+ NSCLC	Ph2 Arc-7 topline	905	Domvanalimab is an anti-Tigit MAb, Fc-silent; Roche's Skyscraper-01 failed
Fazirsiran (ARO-AAT/TAK-999)	Arrowhead/ Takeda	Alpha-1 antitrypsin deficiency	Ph2 Sequoia	743	RNAi therapeutic

Big biotech's Q4 clinical catalysts					
PRA023	Prometheus	UC, Crohn's disease	Ph2 topline Artemis-UC, ph2a Apollo-CD full data	489	Anti-TL1A MAb (*Prometheus takes on Pfizer in inflammatory bowel diseases*)
Bezuclastinib	Cogent Biosciences	Advanced systemic mastocytosis	Ph2 Apex additional data (open-label study)	418	Proto-oncogene c-Kit (CD117) inhibitor, similar MoA to Blueprint's Ayvakit
TransCon CNP	Ascendis	Achondroplasia (aged 2-10)	Ph2 Accomplish	343	See text
Sitravatinib + Opdivo	Mirati	2L/3L non-squamous NSCLC	Ph3 Sapphire, interim OS	341	Combination powered to show 3.5-month OS benefit vs docetaxel (SVB)
Auvelity (AXS-05)	Axsome	Alzeimer's disease agitation	Ph3 Accord, randomised withdrawal study	326	Primary endpoint is time from randomisation to relapse of agitation symptoms (up to 26 weeks), FDA approved in MDD
EDIT-301	Editas	Sickle cell disease	Ph1/2 Ruby (1st patient)	295	Crispr/Cas12a gene-edited cell therapy targeting beta-globin, expect data on safety, engraftment, and haematological parameters
Seralutinib (GB002)	Gossamer Bio	Pulmonary arterial hypertension	Ph2 Torrey in patients with PAH whose disease has progressed despite SoC; Nov/Dec	262	Inhaled PDGFR, CSF1R and c-KIT Inhibitor, Gossamer has had several pipeline setbacks (*Gossamer hangs by a thread*)
Zoryve (roflumilast cream)	Arcutis	Atopic dermatitis	Ph3 Integument-1, Integument-2	171	Approved in plaque psoriasis
Vudalimab (XmAb20717) +/- chemo or Lynparza	Xencor	mCRPC	Ph2, possibly at SITC	117	PD-1xCTLA-4 bispecific
PTC923	PTC Therapeutics	PKU	Ph3 Aphenity	60	Synthetic prodrug of tetrahydrobiopterin (BH4), similar mechanism to Biomarin's approved Kuvan
REGN5458	Regeneron	R/R multiple myeloma	Ph1/2 potentially pivotal	-	BCMAxCD3 bispecific
ALN-APP	Alnylam/ Regeneron	Early onset Alzheimer's disease	Ph1	-	RNAi therapeutic targeting amyloid precursor protein
VAX-24	Vaxcyte	Prevention of invasive pneumococcal disease in adults	Ph1/2 vs Prevnar 20 in Oct/Nov	-	24-valent vaccine, Pfizer's 20-valent Prevnar 20 dominates
					Anti-complement C3 antibody similar to

NGM621	NGM	Geographic atrophy	PhII		antibody similar to Apellis's pegcetaloplan, which has a Pdufa in November

Source: Evaluate Pharma, company releases & clinicaltrials.gov.