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Key biotech catalysts approach

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Important clinical data are expected in the fourth quarter from biotech companies including Madrigal, Arena, Rhythm and Forma.

While oncology readouts dominate for big pharma players, the focus for biotech is more varied. Here *Evaluate Vantage* looks at important events due for companies with a market cap of $1bn and above.

The Ash conference in December focuses on haematological malignancies, with early data from Forma, Kura and Trillium expected. Arena will report atopic dermatitis results while Rhythm hopes to expand the use of its obesity project in various genetic forms of the disorder. Madrigal, meanwhile, hopes to tackle fatty liver disease.

The **Madrigal** data are from the open-label arm of the phase III Maestro-NAFLD-1 trial, where around 100 patients were given 100mg of **resmetirom** daily. 16-week results are expected from non-invasive tests including MRI-PDFF, fibrosis biomarkers, liver enzymes, and atherogenic lipids and lipoproteins.

Resmetirom is a thyroid hormone receptor-β agonist, a mechanism also being investigated by Viking Therapeutics. As a benchmark for Madigal's upcoming data, albeit at 12 weeks, Viking's VK2809 showed median change from baseline liver fat content of -53.8% to -59.7% across three treatment arms, versus -9.4% for placebo in a phase IIa NAFLD study.

Madrigal's upcoming resmetirom results will read through to its registrational Maestro Nash study, data from which are now due in the second half of next year owing to enrolment delays due to Covid-19.

A bigger indication

Rhythm's setmelanotide, a melanocortin 4 agonist, is already filed in two rare genetic obesity indications, pro-opiomelanocortin deficiency obesity and leptin receptor deficiency obesity, with a US action date in November.

To broaden the project's reach data are expected towards the end of the year or early 2021 in Alstrom syndrome and Bardet-Biedl syndrome, two rare genetic disorders where sufferers experience an insatiable hunger, also known as hyperphagia, and severe obesity beginning early in life. Stifel analysts note that Bardet-Biedl is the main value driver, with ~5,000 patients globally.

The pivotal trial is in 30 patients and the primary endpoint is the proportion of patients who achieve a ≥10% reduction from baseline in body weight after ~52 weeks' treatment. A 14-week double-blind placebo-controlled period is followed by a 38-week open-label stage.

In a phase II open-label basket study, the mean change in body weight from baseline at 12 months was -16.3% in seven Bardet-Biedl patients. The most common adverse event was injection-site reaction.

A first

In the fourth quarter **Arena's etrasimod** will yield data from its first foray into dermatology. The phase IIb Advise study in 120 atopic dermatitis sufferers tests two doses, with a 12-week treatment period followed by four weeks' observation.

The primary endpoint will assess percent change in eczema area and security index (EASI) from baseline to week 12. Secondary measures include EASI-75.

Looking at the competition, Sanofi/Regeneron's market leader, Dupixent, has shown placebo-adjusted 16-week EASI-75 of 32-36%. Abbvie's Jak inhibitor Rinvoq, meanwhile, has shown results of 64% with its higher dose in phase III.

Etrasimod is an S1P receptor modulator like Bristol's Zeposia, which is approved in relapsing-remitting multiple sclerosis and in late-stage trials in ulcerative colitis and Crohn's disease; however, it does not look to be in development for atopic dermatitis.

Etrasimod's lead and most valuable indication is ulcerative colitis, but investors will have to wait until the end of next year for data from two phase III studies.

Conference data

Forma Therapeutics managed a $319m IPO in June, and phase I data are expected at Ash from ascending doses of its sickle cell disease project **FT-4202**.

At EHA back in June, a single 700mg dose of FT-4202 showed a median 10.2mmHg reduction in the point of sickling in three subjects after 24 hours. The trial also enrols healthy volunteers and has a placebo cohort. Only grade 1 adverse events were seen, but palpitations did occur in one sickle cell disease patient about eight hours after a single dose, something to watch for with the upcoming data.

FT-4202 is a pyruvate kinase R (PKR) activator much like Agios's mitapivat. Multiple ascending-dose data from the latter are also due at Ash, after results were toplined earlier at EHA. Focus here will be on the previously disclosed vaso-occlusive crises that were possibly related to treatment with mitapivat.

Although it is too early to call a winner Leerink analysts believe that FT-4202 could become the best-in-class PKR drug thanks to its longer half-life, potentially allowing once-daily dosing, and no off-target aromatase impact, which has been evident with mitapivant preclinically.

The following table notes additional fourth-quarter events for biotech, and includes consensus forecasts from *EvaluatePharma*. A further analysis covering companies with a market cap below $1bn will follow.

Selected Q4 events (excludes Covid-19 data)					
Project	**Company**	**Therapy area**	**Q4 event**	**2026e indication sales ($m)**	**Note/Vantage coverage**
COR388 (atuzaginstat)	Cortexyme	Alzheimer's (mild to moderate)	Interim from Ph2/3 Gain	1,530	*Alzheimer's catalysts round off a year dominated by Biogen*
MGL-3196 (resmetirom)	Madrigal	NAFLD (Nash and fibrosis)	Data open-label arm of Ph3 Maestro-NAFLD-1	1,026	See text
RP-A501	Rocket	Danon disease	Ph1	887	Gene therapy for often fatal disease owing to rapidly progressive heart failure
Setmelanotide	Rhythm	Alstrom syndrome & Bardet-Biedl syndrome	Pivotal Ph3 (Q4/early Q1 2021)	799*	See text

Selected Q4 events (excludes Covid-19 data)					
ARO-AAT	Arrowhead	AAT-associated liver disease	6-mth liver biopsies from AROAAT2002 (open-label; AASLD, Nov 13-16)	688	*Arrowhead gets a $1.4bn boost from flattering data*
APL-2 (pegcetacoplan)	Apellis	PNH	Pegasus, 48 week data	554	16-wk data showed APL-2 beating Alexion's Soliris; *Pegasus flies for Apellis, up to a point*
Xywav	Jazz	Idiopathic hypersomnia	Ph3	420*	Leerink: IH prevalence population is at least as large as narcolepsy (US approved)
VGX-3100	Inovio	HPV-associated cervical dysplasia	Pivotal Reveal-1	370	Provide read-through to Reveal-2; results from both needed for BLA filing; Reveal-2 primary completion Apr 21
RGX-314	Regenexbio	Wet AMD	Interim ph2 AAViate (vs Lucentis)	263	Gene therapy delivered via suprachoroidal injection, more convenient than subretinal (surgical)
Voclosporin Ophthalmic Solution	Aurinia	Dry eye syndrome	Ph2/3 Audrey	209	Previous Ph2 showed superiority vs Restasis, Pdufa in Jan for lupus
TTI-621, TTI-622	Trillium	r/r haematologic malignancies/multiple myeloma	Further ph1, (Ash, Dec 5-8)	202	CD47 blocking fusion proteins. *Trillium makes the most of Pfizer's tentative approach*
Etrasimod	Arena	Atopic dermatitis	Ph2b Advise	151	See text
Vynpenta (avacopan)	Chemocentryx/ Vifor	Hidradenitis suppurativa	Ph2b Aurora	72	Filed in ANCA - associated vasculitis. In HS Inflarx's similarly acting IFX-1 failed last year
KO-539	Kura Oncology	Acute myeloid leukaemia	Ph1 (Ash, Dec 5-8)	65	Menin-MLL inhibitor. Leerink: Interest drawn since Ph1 data for Syndax's SNDX-5613 provided clinical validation
Etranacogene dezaparvovec (AMT-061)	Uniqure/CSL	Haemophilia B	Hope-B pivotal trial, 26 week	49	Pfizer/Roche's rival project fidanacogene elaparvovec is in

(AMT-061)	Selected Q4 events (excludes Covid-19 data)		data		phase III; *No buyout for Uniqure*
TPX-0022	Turning Point	Met+ solid tumors	Initial ph1 data	12	Met/CSF1R/SRC inhibitor. Leerink: focus will be safety/tolerability, as Novartis's Tabrecta had unexpected interstitial lung disease disclosed in the label
ADP-A2M4CD8	Adaptimmune	Lung, EGJ, H&N and bladder cancers	Surpass	-	Updates on dose escalation cohorts expected at a conf; *Adaptimmune surges as it strides out for market*
FT-4202	Forma Therapeutics	Sickle cell disease	Multiple ascending dose data (Ash, Dec 5-8)	-	See text
*Note: *sales by indication data not split out. Sources: Evaluatepharma, clinicaltrials.gov, company releases & analyst notes.*					