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Biotech’s important upcoming data

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Late-stage data are expected for Apellis; Ionis and Biogen tackle ALS; and Mirati awaits combination results.

Evaluate Vantage has delved into upcoming data readouts due in the third quarter for companies with a market cap of $1bn plus, and here Apellis stands out. The group will be hoping its complement inhibitor pegcetacoplan can succeed where others have failed.

Meanwhile, Ionis and Biogen will release late-stage results in amyotrophic lateral sclerosis, an area littered with previous failures, and combination data are due from Mirati’s Kras inhibitor adagrasib in lung and colorectal cancers.

Targeting complement

Apellis is expecting phase 3 data with its intravitreal formulation of **pegcetacoplan** in geographic atrophy, an advanced form of dry age-related macular degeneration. The group believes it can succeed where other complement-targeting agents, such as Roche’s lampalizumab and more recently Gemini's GEM103, have struggled to show a benefit.

Apellis's confidence comes from the project's mechanism of action: by inhibiting C3 pegcetacoplan knocks out all three pathways involved in the complement system. Other experimental agents have tended to inhibit only one pathway, so pegcetacoplan could have a stronger effect, Apellis reckons.

That theory will be put to the test with Derby and Oaks studies, whose primary endpoints are a reduction in the growth of the GA lesion at month 12 with pegcetacoplan versus sham injection. One potential stumbling block could be choroidal neovascularisations, or abnormal blood vessels, which were seen in intravitreal pegcetacoplan’s phase 2 trial, Filly. Another worry is patients missing doses due to Covid-19 disruption.

If intravitreal pegcetacoplan does succeed, it could have the GA market to itself for a while. *Evaluate Pharma*'s consensus forecasts that the project will bring in $1.2bn in 2026.

Kras combinations

Amgen’s Kras G12C inhibitor Lumakras gained an early US approval in second-line lung cancer in May, and now **Mirati** is gearing up for data with its similarly acting **adagrasib**. The phase 1/2 Krystal-1 study is combining adagrasib plus Keytruda in NSCLC, and adagrasib plus Erbitux in colorectal cancer; updated monotherapy and initial combination results are expected next quarter.

So far, adagrasib monotherapy has bested Lumakras in terms of efficacy. At last year's Triple meeting adagrasib showed an overall response rate of 45% in NSCLC, versus 37% in Lumakras's phase 2 Codebreak-100 study.

However, at present Amgen has the larger dataset and the edge when it comes to safety. 14% of adagrasib-treated patients suffered QT prolongation which carries a risk of sudden cardiac death, an issue that has not been seen with Lumakras.

Mirati plans to file for accelerated approval in second/third line NSCLC in the second half of the year.

ALS hopeful

The next big readout in ALS will concern the phase 3 study of tofersen, which Biogen licensed from Ionis in 2018. The field desperately needs a win; recent failures include Brainstorm Cell Therapeutics' cell therapy NurOwn and Orphazyme's arimoclomol *(Arimoclomol failure leaves Biogen/Ionis exposed, May 7, 2021)*

Tofersen is an antisense medicine targeting superoxide dismutase 1 (SOD1). A mutation in the SOD1 gene is the genetic driver in approximately 2% of ALS cases – this is thought to cause misfolded proteins leading to degeneration of motor neurons.

The Valor study has three segments, and it is part C, testing a 100mg dose, that will yield data. The study includes 99 patients with a confirmed SOD1 mutation, and the primary efficacy endpoint is change from baseline in ALSFRS-R total score, a measure of disability, at week 28.

Data from parts A and B, which tested ascending doses of tofersen, showed a knockdown of cerebrospinal SOD1 protein, which was highest with the 100mg dose. There were also benefits on the ALSFRS-R scale, with a 1.19-point decrease with the 100mg dose versus a 5.63-point fall with placebo. A lower score represents worsening function.

A phase 3 in presymptomatic SOD1 ALS patients called Atlas is also under way.

The table below contains a fuller list of upcoming catalysts with consensus forecasts from *Evaluate Pharma*. A look at big pharma clinical catalysts can be found here.

Q3 clinical catalysts (excludes Covid-19 data)					
Product	**Company**	**Therapy area**	**Q3 clinical catalyst**	**2026e indication sales ($m)**	**Note/Vantage coverage**
Adagrasib	Mirati	NSCLC, colorectal cancer	Ph1/2 Krystal-1 monotherapy data and combination data (+Keytruda in NSCLC, + Erbitux in CRC)	1,608	See text
Repotrectinib	Turning Point/Zai Lab	Solid tumours (harbouring ALK, ROS1, or NTRK1-3 rearrangements)	Enrollment and data update from Ph2 Trident-1 in H2	1,364	Need to see evidence of durability *(Turning Point on the straight track, but to where?)*
APL-2 (intravitreal pegcetacoplan)	Apellis	Geographic atrophy secondary to AMD	Ph3 Derby and Oaks	1,184	See text
AXS-05	Axsome	Treatment resistant depression	Ph2 Merit H2	893*	Vs placebo, the first study Stride-1 against bupropion failed *(Axsome trips up)*, Pdufa in August for major depressive disorder

Q3 clinical catalysts (excludes Covid-19 data)					Timing guided to
Brukinsa (zanubrutinib)	Beigene	1L CLL	Ph3 Sequoia (zanubrutinib vs bendamustine + rituximab)	821	2021, CLL market dominated by Imbruvica
Anavex 2-73 (blarcamesine)	Anavex	Rett syndrome	Ph2/3 Excellence H2 paediatric	521	Potentially pivotal study, still waiting for results from Avatar study in adult Rett syndrome, guided to mid year
Ampreloxetine (TD-9855)	Theravance	Symptomatic neurogenic orthostatic hypotension	Ph3 Sequoia	348	The company's first wholly-owned asset, encouraging Ph2
SER-287	Seres	Mild-to-moderate ulcerative colitis	Ph2b Eco Reset top line mid year, pharmacology data H2	309	Microbiome modulator
Etrasimod	Arena	Crohn's disease	Ph2 Cultivate dose-ranging data H2	175	Potential readthrough to ongoing Ph3 ulcerative colitis studies due early 2022
Zanidatamab	Zymeworks	1L Her2 expressing gastroesophageal adenocarcinoma	Ph2 plus chemo, H2	146	Keytruda's approval was based on Keynote-811 interim: Keytruda + Herceptin + chemo demonstrated an ORR of 74% (vs. 52% placebo) and a mDOR of 10.6 months (vs. 9.5 months)
Tofersen (BIIB067)	Ionis/Biogen	ALS	Ph3 Valor H2	138	See text
RGX-314 suprachoroidal	Regenxbio	Wet AMD	Safety data ph2 AAViate (vs Lucentis)	90	Anti-VEGF gene therapy, Adverum's therapy had a toxicity scare (*Adverum halt raises more gene therapy questions*)
RP-L301, RP-L401	Rocket Pharmaceuticals	PKD, infantile malignant osteopetrosis	Update with RP-L301 in PKD in 2H21, first look at data with RP-L401 in IMO	85, 3	Gene therapies, had been expecting more data with RP-A501 in Danon disease but trial put on clinical hold for

Q3 clinical catalysts (excludes Covid-19 data)					
					hold for additional risk mitigation
Ionis-MAPTRx (BIIB080)	Ionis/Biogen	Mild Alzheimer's disease	Ph1/2 H2	-	Antisense oligonucleotide (ASO) targeting tau
SL-172154	Shattuck Labs	Ovarian cancer	Ph1 dose escalation due H2	-	A dual CD47/SIRPα inhibitor and CD40 agonist, IPO last Oct raised $232m
Izencitinib (TD-1473)	Theravance	Ulcerative colitis	Ph2b/3 Rhea	-	Gut-selective oral pan-JAK inhibitor, the delay with crohn's disease data to Q4 has pushed out timeline for JNJ opt-in decision until Q1
OP-1250	Olema Oncology	HR+/HER- breast cancer	Ph1 initial data	-	Completed $240m IPO last Nov, OP-1250 is a complete estrogen receptor antagonist, Sanofi has the most advanced project amcenestrant
INCB86550	Incyte	Solid tumours	Ph1	-	Oral PD-L1

**Includes forecasts for major depressive disorder. Sources: Evaluate Pharma, company releases, analyst notes & clinicaltrials.gov.*