Evaluate Vantage

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Biotech’s important data reveals

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Key upcoming clinical results approach in the third quarter for lecanemab, high-dose Eylea and Zimura.

After combing through big pharma's upcoming data reveals, here *Evaluate Vantage* looks at the clinical results due for biotech companies with a market cap of $1bn and above.

The third quarter will see the start of the big beta-amyloid MAb readouts, with Biogen and Eisai set to report phase 3 data with their contender lecanemab in the autumn. And Regeneron/Bayer’s defence of Eylea begins with data on its high-dose, long-acting project, while Iveric Bio will be hoping for a second late-stage hit with Zimura in geographic atrophy.

Alzheimer challenge

The primary measure of **Biogen/Eisai’s** Clarity-AD study is change from baseline in the clinical dementia rating-sum-of-boxes (CDR-SB) at 18 months, with **lecanemab** against placebo in patients with early Alzheimer’s disease.

A look at the earlier Study 201, under which lecanemab was submitted for accelerated approval, does not instil much confidence in the upcoming Clarity-AD readout.

201 failed to meet its primary endpoint, change from baseline in Alzheimer's disease composite score; however, a Bayesian analysis suggested that lecanemab was associated with 26% less decline than placebo on CDR-SB.

It is likely that US regulators will wait for the Clarity-AD results before issuing a verdict on lecanemab.

The next beta-amyloid MAb set to yield data is Lilly’s donanemab, with a head-to-head trial versus Aduhelm due to read out in the second half, ahead of the phase 3 Trailblazer-Alz 2 in mid-2023. Towards the end of this year there should also be results with Roche’s gantenerumab.

Another anti-amyloid MAb, Roche and AC Immune’s crenezumab, recently failed a mid-stage trial in presymptomatic patients with a specific mutation, providing another dent to the amyloid hypothesis.

Plan of defence

Developing a **high-dose, long-acting Eylea** is **Regeneron** and **Bayer’s** plan for defending their blockbuster eye drug against biosimilars and Roche‘s new bispecific antibody Vabysmo. The aim is to show non-inferiority

to 2mg Eylea, the current recommended dose, while being administered less frequently.

The second half of the year will see data from two studies: the phase 3 Pulsar in wet AMD, and the phase 2/3 Photon in diabetic macular oedema. Both trials test 8mg Eylea dosed every 12 or 16 weeks versus 2mg Eylea given every 8 weeks; each arm also includes a loading dose. The primary endpoint for both is the mean change in best corrected visual acuity (BCVA) at week 48.

An earlier wet AMD study called Candela showed an improvement of 7.9 letters for the high-dose group versus a 5.1-letter gain with standard Eylea at 44 weeks; the difference was not statistically significant.

However, in the 8mg cohort there were two retinal tears and four cases of vitreous detachment, versus none and two respectively in the 2mg arm. Overall, rates of adverse events were similar between the two treatment groups, and there were no cases of serious intraocular inflammation.

Questions remain over the commercial prospects for the high-dose version and whether it also needs to show superiority to gain a foothold in the market, particularly once biosimilars are available. Eylea's patents start to expire next year.

Repeat success?

With the complement C5 inhibitor **Zimura**, **Iveric Bio** hopes to take on Apellis in geographic atrophy.

Previously, the phase 2/3 Gather1 study of Zimura met its primary endpoint, showing a statistically significant 27% reduction in GA growth over 12 months, which was persistent at 18 months. Zimura was well tolerated and there was no inflammation; however, there was an increased incidence of choroidal neovascularisations, or new blood vessels, with Zimura versus placebo.

The second study, Gather2, is testing 2mg Zimura and has the same endpoint as Gather1.

Apellis is ahead in this space, having recently submitted its C3 inhibitor intravitreal pegcetacoplan to the FDA. However, that company's clinical program had mixed results, showing a hit in one phase 3, but then a miss in the second at 12 months. Pooling the data did result in statistically significant hits, but it is unclear whether the FDA will accept this approach.

It is important to note that Iveric Bio's studies only include non-foveal patients, an earlier stage of disease, while Apellis also enrolled foveal patients.

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

Clinical catalysts in Q3 2022, market cap $1bn+					
Project	**Company**	**Therapy area**	**Q3 clinical catalyst**	**2028e indication sales ($m)**	**Note/Vantage coverage**
Eylea (high-dose, long-acting)	Regeneron/Bayer	Neovascular age-related macular degeneration & diabetic macular oedema	8mg dose ph 3 Pulsar in wet AMD, ph 2/3 Photon in DME H2	5,133*	See text
Padcev +/- Keytruda	Seagen/ Astellas	1L chemo-ineligible metastatic urothelial cancer	Topline ph2 Cohort K of EV-103/Keynote-869	4,815*	On the market for 3L, cohort K data could allow accelerated approval
NTLA-2001	Intellia/ Regeneron	ATTR-cardiomyopathy	Ph1 interim data H2	1,980 (as amyloidosis)	Crispr/Cas9 therapy, seen TTR reduction already in polyneuropathy, still waiting for Alnylam's Onpattro data from Apollo-B
KarXT	Karuna	Schizophrenia	Ph3 Emergent-2	1,926	*Karuna seeks a novel*

Clinical catalysts in Q3 2022, market cap $1bn+					
karXT	Karuna	Schizophrenia	Q3	1,926	*schizophrenia mechanism*
Lecanemab (BAN2401)	Biogen/Eisai	Early Alzheimer's disease	Ph 3 Clarity AD confirmatory study, due September	1,632	See text
ARV-471	Arvinas/Pfizer	2/3L postmenopausal ER+/HER2- breast cancer	Ph2 Veritac expansion cohort (mono 200mg and 500mg), safety data, ph1b combination cohort with Ibrance H2	1,310	Oral Serd, efficacy in pretreated setting looks driven by ESR1 mutations (*Close encounters of the Serd kind*)
Zimberelimab +/- domvanalimab +/- etrumadenant	Gilead/ Arcus	1L PD-L1 50%+ NSCLC	Ph2 PFS Arc-7	905 (for domvanalimab)	Domvanalimab (anti-Tigit MAb, Fc-silent), 3rd interim analysis showed improving ORR, Roche's Skyscraper-01 failed (*Arcus sets the hopes for Tigit in lung cancer*)
ARO-AAT (TAK-999)	Arrowhead/ Takeda	Alpha-1 antitrypsin deficiency	12-month biopsy data from Ph2 Sequoia in the autumn	750	RNAi therapeutic
Zimura	Iveric Bio	Geographic atrophy secondary to age-related macular degeneration	Ph3 Gather2	476	See text
NTLA-2002	Intellia	Type 1 or type 2 hereditary angioedema	Ph1/2 H2	290	Crispr/Cas9 therapy to inactivate KLKB1 gene (encodes for prekallikrein), Ionis's donidalorsen (prekallikrein antisense) is in ph3
Vudalimab (XmAb20717) +/- chemo or Lynparza	Xencor	mCRPC	Ph2	64	PD-1xCTLA-4 bispecific
BLU-945 + Tagrisso	Blueprint	EGFR-mutant NSCLC	Ph1/2 Symphony dose escalation cohort	-	Data at AACR showed dose-dependent trends on tumour shrinkage & circulating tumour DNA (monotherapy)

Already on the market in different indications. Source: Company press releases, Evaluate Pharma 24 June.

Clinical catalysts in Q3 2022, market cap $1bn+

Check out our podcast discussing third quarter catalysts here.