Evaluate Vantage

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Second-quarter catalysts for the smaller players

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Key catalysts approach for Orphazyme, Gemini and Immutep.

After delving into the key clinical events due for big pharma and biotech companies, *Evaluate Vantage* here looks at smaller players − those with a market cap of under $1bn.

Orphazyme's recent setback with arimoclomol in a muscle-wasting disease puts a damper on upcoming data in amyotrophic lateral sclerosis (ALS). Meanwhile, Gemini's new approach to geographic atrophy will yield data, and Immutep hopes to rebound with results on its Lag3 project eftilagimod alpha.

Setbacks

The news last week that Orphazyme's lead project arimoclomol had failed in a phase 2/3 study in inclusion body myositis (IBM) caused shares to plummet 30%. The stumble, not the first for arimoclomol, leaves questions marks over the company's next data readout in ALS, due in the second quarter. The project is one of the most advanced in the ALS pipeline following the failure of Brainstorm's NurOwn last year.

The 245-patient phase 3 study is testing 400mg of oral arimoclomol three times daily, versus placebo, for 18 months. The primary endpoint is the combined assessment of function and survival, which ranks patients' clinical outcomes based on survival time and change in the ALS Functional Rating Scale-Revised (ALSFRS-R).

The same dosing was used in the failed IBM study, but Orphazyme was keen to point out the differences between the two diseases, noting IBM is a progressive muscle-wasting disorder while ALS is a neurodegenerative disease.

But arimoclomol, which is thought to work by stimulating heat-shock proteins, missed the endpoints of a registrational study in Neimann-Pick disease type C, a rare inherited condition that causes progressive neurodegeneration and death. Nonetheless the FDA has accepted a filing for the project, perhaps swayed by signs of disease stabilisation or a lack of options for NPC; arimoclomol has a Pdufa date here of June 17.

Gemini's complement approach

Geographic atrophy, an advanced form of age-related macular degeneration, has proven another difficult disease to crack. Gemini Therapeutics, which went public via the Spac route in February, will soon find out if it has a chance here: phase 2 data on its lead project, GEM103, are due this quarter.

Like others in the space, Gemini is hitting the complement cascade. However, GEM103 works differently to

other projects in development, being a recombinant form of complement factor H (CFH), a modulator of the alternative complement pathway.

The single-arm phase 2a Regatta study is testing repeat intravitreal injections of GEM103 in 60 patients with dry AMD and loss of function CFH variants. This population makes up around 40% of geographic atrophy patients.

The main purpose of the trial is to inform the design of an upcoming sham-controlled phase 2b study, but investors will be looking for clues about whether the group's novel approach works.

Stifel analysts want to see three things: clean safety, with a close eye on choroidal neovascularisations; consistent and durable biomarker reductions; and possibly favourable efficacy – the study is assessing lesion growth and best corrected visual acuity. Still, any data here could be difficult to interpret given the lack of a placebo arm.

Choroidal neovascularisations are new, damaging blood vessels that are seen in wet AMD. They are under the spotlight after being observed in the phase 2 Filly study of another geographic atrophy contender, Apellis's C3 inhibitor pegcetacoplan. That group's pivotal trials, Derby and Oaks, are set to yield data in the third quarter.

Lag3 laggard

Lag3's potential in immuno-oncology was crystallised last month when Bristol Myers Squibb's Relativity-047 study showed the anti-Lag3 MAb relatilimab to boost the activity of Opdivo in front-line melanoma. One of the beneficiaries was Australia's Immutep, a Lag3-focused biotech whose stock spiked 30%.

But the shares have fallen back as two 2021 catalysts near for Immutep's own eftilagimod alpha, a soluble Lag3 dimer. These comprise a second overall survival readout from the AIPAC paclitaxel-combo breast cancer trial, and data from TACTI-002, a solid tumour study in combination with Merck & Co's Keytruda.

Immutep will have to hope that the data improve as AIPAC matures: its first OS assessment found a 17% reduction in risk of death versus paclitaxel alone, but this was not significant, with a p value of 0.140.

TACTI-002 comprises first-line and PD-(L)1-refractory NSCLC, and head and neck cancer, where so far the combo has yielded remission rates of 39%, 4% and 43% respectively. A major caveat is that TACTI-002 is uncontrolled, so any comparison will be against Keytruda monotherapy on a cross-trial basis.

Eftilagimod, one of Immutep's four Lag3 approaches, works on the basis that Lag3 itself can activate antigen-presenting cells. Leramilimab (IMP701/LAG525) is an antagonist analogous to relatlimab and licensed to Novartis; the agonist MAb IMP761, and the depleting MAb IMP731 (licensed to Glaxosmithkline as GSK2831781) are for autoimmune diseases.

The table below contains a fuller list of upcoming catalysts with consensus forecasts from *Evaluate Pharma. Evaluate Vantage* has previously looked at clinical data expected for big pharma and biotech companies.

Q2 clinical catalysts (excludes Covid-19 data)					
Product	**Company**	**Therapy area**	**Q2 clinical catalyst**	**2026e indication sales ($m)**	**Note/*Vantage coverage***
ACI-24	AC Immune	Alzheimer's disease	Ph2 18-month data	1,606*	Focus on safety & tolerability
Anavex 2-73 (blarcamesine)	Anavex	Rett Syndrome	Ph2 Avatar, adults (Aus); ph2/3 Excellence, paediatric	568	Ph2 US trial met primary and secondary endpoints
Vamorolone	Santhera	Duchenne muscular dystrophy	Topline 6mo data Ph2b Vision-DMD pivotal trial	450	Vam vs prednisone vs placebo
Eftilagimod alpha	Immutep	Breast cancer/ NSCLC/head & neck	Ph2b AIPAC OS data, further data from TACTI-002 (+ Keytruda)	440	See text
		Relapsed/refractory	Ph1 Augment		Oral menin inhibitor, rival to

Q2 clinical catalysts (excludes Covid-19 data)					
SNDX-5613	Syndax	Relapsed/refractory leukaemias	Ph1 Augment-2	407	Kura's KO-539 (*Ash 2020 – Kura looks to take on Syndax*)
SB206	Novan	Molluscum contagiosum	Ph3 B-Simple4	358	Topical antiviral
Losmapimod	Fulcrum	Facioscapulohumeral muscular dystrophy	ReDUX4 data in 80 patients	295	At interim look biopsy data did not show a separation from placebo (*Fulcrum's biopsy conundrum*)
Arimoclomol	Orphazyme	ALS	Ph3	289	See text
Plinabulin	Beyondspring	NSCLC	Final data from Dublin-3	284	+ docetaxel in 2/3L NSCLC
Lenabasum	Corbus	Dermatomyositis	Ph3 Determine	189	Failed in systemic sclerosis and cystic fibrosis
ADP-A2M4	Adaptimmune	Synovial sarcoma	Ph2 Spearhead-1 preliminary data at Asco	149	Mage A4 TCR therapy, prior safety issues (*More deaths raise further questions about Adaptimmune*)
Reproxalap ophthalmic solution	Aldeyra	Allergic conjunctivitis	Ph3 Invigorate top line	106	Dry eye data not expected until H2
IFX-1 (vilobelimab)	Inflarx	ANCA-associated vasculitis	Ph2 Ixplore final due mid year	90	Project failed in hidradenitis suppurativa (*Inflarx pushes past the red flags to claim a win*)
STRO-002	Sutro	Ovarian cancer	Ph1 updated dose-escalation data	88	Anti-FRα MAb-drug conjugate, promising early data but issues with neutropenia (*Sutro bucks the folate trend*)
Oral Korsuva	Cara	Pruritis in atopic dermatitis patients	Ph2 Kare	30	Oral missed secondary endpoint in CKD, IV has Aug Pdufa in haemodialysis pts with pruritis (*Big placebo response rattles Cara ahead of pivotal tests*)
GEM103	Gemini	Dry AMD patients with CFH loss-of-function gene variants	Ph2 Regatta	-	See text

** $1,496m assigned to undisclosed partner sales. Sources: EvaluatePharma, company releases, analyst notes & clinicaltrials.gov.*