Evaluate Vantage

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Key data reveals for the small players

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Praxis, Proqr and Nordic Nanovector are awaiting important data.

Evaluate Vantage has already previewed important upcoming first quarter data for big pharma and larger biotech groups. Now it is the turn of companies with a market cap of under $1bn.

Nordic Nanovector is finally set to deliver data with its much-delayed CD37 project Betalutin, while Proqr's antisense project sepofarsen will set out its efficacy in a rare inherited eye disorder. Praxis, meanwhile, is hoping to jump on Sage/Biogen's bandwagon with PRX-114, a Gaba A modulator in major depressive disorder.

PRX-114 is **Praxis Precision Medicine**'s most advanced project. Two studies will report in the first half of 2022: the phase 2/3 monotherapy trial Aria, and the dose-ranging phase 2 adjunctive study Acapella.

Aria is the first of two registrational studies and tests PRX-114 versus placebo, with 40mg of drug given once daily for 28 days. The primary endpoint is change from baseline in total score on the 17-Item Hamilton Depression Rating Scale (Ham-D17) at day 15.

Acapella is testing daily doses of 10mg, 20mg, 40mg or 60mg of PRX-114 for 28 days versus placebo in patients who have had an inadequate response to antidepressant treatment. Ham-D17 at day 15 is the primary measure.

Investors will be watching to see how the Aria data compares with Biogen/Sage's Gaba A modulator zuranolone, a rolling submission for which is expected to start early next year. Zuranolone's monotherapy trial, Waterfall, met significance, but efficacy was only modest, with a 1.7-point placebo-adjusted change on Ham-D17 at day 15. While zuranolone dosing stopped after 14 days, Praxis is continuing dosing of PRX-114 to day 28.

Side effects in the Waterfall study included somnolence, dizziness and sedation. Safety will thus be another crucial point for Praxis's Aria study.

Proqr's antisense

Leber congenital amaurosis type 10 (LCA10) is a rare inherited eye disorder caused by mutations in the CEP290 gene. Pivotal data are expected from **Proqr's sepofarsen**, an antisense project that binds to CEP290 RNA to enable correct splicing and production of the CEP290 protein.

Due in late Q1 or early Q2 are the results from the phase 2/3 Illuminate study. 36 patients aged eight and older

are given an intravitreal injection of sepofarsen at the target registration dose (80µg/160µg loading dose), low dose (40µg/80µg loading dose) or sham comparator.

After the initial loading dose, maintenance doses are given at month three and then every six months. After 12 months treatment of the contralateral eye can be started. The primary endpoint is the mean change from baseline in best-corrected visual acuity (BCVA) at 12 months.

In a phase 1/2 study six patients given the target registration dose showed a mean change from baseline in BCVA of 0.93 logMAR at 12 months. Proqr notes that this is approximately equivalent to an improvement of nine lines or 45 letters.

Proqr's earlier data look impressive, albeit in small number of patients. Editas's competing project, EDIT-101, which is based on Cripsr gene editing, reported a mixed bag of results from five patients in a phase 1/2 study.

The best performing patient showed a 0.7logMAR improvement in BCVA versus control eye at six months *(Editas falls well short of Brilliance, September 30, 2021).* Longer term data and results from higher doses could come from Editas mid-year, and will prompt comparisons to Proqr.

Delay dismay

It has been a long time coming, but the first half of 2022 should finally see preliminary three-month data from **Nordic Nanovector**'s Paradigme trial of **Betalutin** in follicular lymphoma.

Previously expected by the end of 2021, which was also later than planned, timelines were extended due to slow enrolment and the Covid-19 pandemic. As of November the company reported that 102 of a targeted 120 patients had been signed up.

Paradigme is a single-arm study in third-line CD20-refractory follicular lymphoma. The primary endpoint is overall response rate.

Betalutin targets CD37 with the radionuclide lutetium-177. Several other CD37 targeting approaches are in the clinic, including Genmab/Abbvie's dual-epitope MAb GEN30009 and Debiopharm's antibody-drug conjugate naratuximab emtansine. Phase 2 data from the latter in combination with Rituxan showed an ORR of 44.7% and 24 complete responses in 76 DLBCL patients.

As Betalutin is Nordic's only clinical stage project, investors are desperate for positive data and are unlikely to tolerate any further delays.

The table below contains a fuller list of upcoming catalysts.

Clinical catalysts in early 2022 (excludes Covid-19 data)				
Product	**Company**	**Therapy area**	**Clinical catalyst**	**Note/Vantage coverage**
AVR-RD-01	Avrobio	Fabry disease	Ph1 and Ph2 Fab-GT efficacy data due at World Symposium Feb 2022	Gene therapy. Note recent data from 4D, Sangamo, and Freeline (*Freeline's Fabry data fall short*)
Momelotinib	Sierra Oncology	Myelofibrosis	Ph3 Momentum February	Jak1, Jak2 & ACVR1 inhibitor, via Gilead (ex YM Biosciences)
Rubraca	Clovis	1L ovarian cancer maintenance	Ph3 Athena, data from monotherapy arm Q1	Label extension. Lynparza & Zejula are already well entrenched in 1L ovarian cancer maintenance
PRAX-114	Praxis Precision Medicines	Major depressive disorder	Ph2 Acapella, for adjunctive treatment, Ph2/3 Aria monotherapy Q1	See text
Tavo + Keytruda	Oncosec	Melanoma	Ph2b Keynote-695	Electroporation-delivered IL-12 gene therapy aiming to turn "cold" tumours immunogenic; improving dataset reported at last year's SITC

Clinical catalysts in early 2022 (excludes Covid-19 data)				
Keytruda			topline Q1	(*SITC 2020 – Oncosec's investment case sweetens slightly*)
CX-2009 (praluzatamab ravtansine)	Cytomx	HR+ HER2- breast cancer and TNBC	Ph2 initial data from first two arms of monotherapy Q1	Watch for ocular toxicities
AMT-101 + anti-TNFa	Applied Molecular Transport	Ulcerative colitis, pouchitis	Ph2 Market (UC), Fillmore (pouchitis), Lombard monotherapy (UC) Q1	IL-10 agonist
TP-03	Tarsus	Demodex blepharitis	Ph3 Saturn-2 Q1	Saturn-1 was positive, file pending Saturn-2 data (*Tarsus eyes a new market*)
Sepofarsen (QR-110)	Proqr	Leber's congenital amaurosis	Ph2/3 pivotal Illuminate, late Q1/early Q2	See text
Ganaxolone (oral)	Marinus	Status epilepticus	Ph3 Raise H1	Pdufa in March for CDKL5 deficiency disorder, a rare genetic epilepsy
CA-4948 + Imbruvica	Curis	NHL	Ph1 H1 at medical meeting	Irak-4 inhibitor; Curis expects to have 10-20 AML/MDS patients with SF3B1 or U2AF1 spliceosome mutation enrolled by year-end 2021; potential toxicity concerns (*EHA 2021 movers – more fallers than risers*)
Betalutin	Nordic Nanovector	NHL	Ph2b Paradigme 3-month readout postponed to H1 from end of 21	See text
DAY101	Day One	Paediatric glioma	Ph2 Firefly-1 H1	Pan-Raf inhibitor originated at Biogen, which licensed it to Takeda; it was then acquired by Day One
Atrasentan	Chinook	Glomerular diseases	Ph2 Affinity H1 basket trial (IgAN patient cohort)	Initial proteinuria data should provide investors with a preview of atrasentan's profile before topline data from Align ph3 study in IgA nephropathy, expected in 2023
ATH-1017	Athira	Alzheimer's disease	Ph2 Act-AD topline H1	Small molecule designed to enhance the activity of hepatocyte growth factor (HGF) and its receptor, MET
NKX101	Nkarta	r/r AML and higher risk MDS	Ph1 H1	NKG2D Car-NK cells
Bezuclastinib (CGT9486)	Cogent Biosciences	Advanced systemic mastocytosis	Ph2 Apex prelim data H1 (open label study)	Proto-oncogene c-Kit (CD117) inhibitor (similar MoA to Blueprint's Ayvakit & Bayer's telatinib)
Source: clinicaltrials.gov, Evaluate Pharma & company releases.				

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