Evaluate Vantage

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Snippet roundup: One in, one out in Alzheimer's, but for Lilly oncology is bigger

Edwin Elmhirst

Welcome to your weekly roundup of *EP Vantage's* snippets – short takes on smaller news items.

This week, May 14-18, 2018, we had thoughts on the following: Amgen goes low with migraine drug price; Janssen bows out of Alzheimer's as Lundbeck marches in; Analogic shareholders cry foul; Novartis sweeps out the old for a new start; cure is not a dirty word for Novo Nordisk; phase II awaits for XEN1101, but Xenon's been here before; Cellcentric hopes to succeed where Tokai failed; Beam shines light on new Crispr tech; Lilly shows its hand twice.

These snippets were previously published daily via twitter.

Amgen goes low with migraine drug price

18 May, 2018

It seems that Amgen has learned from previous mistakes, setting a $6,900-per-year price for its newly approved migraine drug, Aimovig. This is lower than the $8,500 that the Institute for Clinical and Economic Review (Icer) recently suggested, setting Amgen and its partner Novartis up to make the most of their first-mover advantage in the anti-CGRP space. Lilly is not far behind with its candidate, galcanezumab, which is due an approval decision by October, while Teva has said its contender, fremanezumab, should be launched by the end of this year despite problems at the Celltrion plant where it is to be manufactured. Aimovig's price tag could also set up a battle against Allergan's Botox, which is approved for the prevention of chronic migraine and costs around $3,500 per year, according to Icer. Amgen and Novartis have also said that Aimovig could cost patients as little as $5 per month via its co-pay programme. All the CGRP inhibitors have a similarly modest effect, reducing monthly migraine days by a couple of days at most. Still, after missteps with the pricing of its PSCK9 antibody, Repatha, at least Amgen has given itself the best chance of convincing payers of Aimovig's value.

Efficacy of the anti-CGRP antibodies

Project	Company	Migraine type	Efficacy vs placebo	Study	Status	2024e sales ($m)
Aimovig (erenumab)	Amgen/Novartis	Episodic	1.1-1.9 days	Arise (NCT02483585); Strive (NCT02456740)	Approved	1,882
		Chronic	2.4 days	Phase II trial (NCT02066415)		
Galcanezumab	Lilly	Episodic	1.8-2 days	Evolve-1 (NCT02614183); Evolve-2 (NCT02614196)	Approval decision due October 2018	927
		Chronic	2 days	Regain (NCT02614261)		
Fremanezumab	Teva	Episodic	1.5 days	Halo EM (NCT02629861)	Approval expected 2018	983
		Chronic	2.5 days	Halo CM (NCT02621931)		
Eptinezumab	Alder	Episodic	0.7-1.1 days	Promise (NCT02559895)	Filing due H2 2018	788
		Chronic	2.6 days	Promise 2 (NCT02974153)		

Source: EvaluatePharma; company presentations

Janssen bows out of Alzheimer's as Lundbeck marches in

18 May, 2018

One in, one out: just as Janssen cans an Alzheimer's candidate Lundbeck takes one into the clinic. Janssen has called off development of its Bace inhibitor atabecestat owing to serious liver enzyme elevations seen in the phase II/III Early trial, which aimed to prove that the project could slow cognitive decline in amyloid-positive asymptomatic people at risk of developing Alzheimer's dementia. Atabecestat, aka JNJ-54861911, was also in a phase II study; this too has been cancelled. Meanwhile Lundbeck, undaunted by the utter failure of any drug to so much as touch Alzheimer's, has waded in with a PDE1 inhibitor, Lu AF76432. It has just started a phase I study in healthy individuals, aiming to identify a maximum tolerated dose. Lundbeck is also developing Lu AF76432 to treat schizophrenia – an easier indication than Alzheimer's, but not by much. At least it does not have much in the way of competition: the only other company looking at PDE1s appears to be Intra-cellular Therapeutics, whose ITI-214 is in phase I trials in neurological conditions including cognitive deficits arising from Parkinson's and Alzheimer's diseases.

PDE1 inhibitors pipeline

Company	Project	Indication	WW indication status
Intra-Cellular Therapies	ITI-214	Parkinson's disease	Phase II
		Congestive heart failure	Phase II
		Other neurological indications, including cognitive deficits arising from Parkinson's and Alzheimer's diseases	Phase I
Intra-Cellular Therapies	ITI-002	Schizophrenia	Phase I
		Other neurological indications	Phase I
		Attention deficit disorder/hyperactivity	Preclinical
		General cardiovascular indications	Preclinical
Lundbeck	Lu AF76432	Alzheimer's disease and schizophrenia	Phase I
Kyoto University	Cancer Research Program	General cancer indications	Research project

Source: EvaluatePharma

Analogic shareholders cry foul

17 May, 2018

A shareholder lawsuit seeking to block Analogic's takeover by private equity for less than its market value was more or less inevitable; the question is whether it will be successful. The imaging group agreed last month to be taken private by Altaris Capital Partners at $84 per share – 13% lower than Analogic's then share price – saying at the time that it had spoken to 75 different potential buyers. Now a lawsuit filed in a Massachusetts federal court, intended to be a class action on behalf of all Analogic's shareholders, alleges that investors were not given enough information about the deal. It seeks to find out more about the nondisclosure agreements that 38 of the 75 potential buyers had with Analogic, including whether they were prohibited from submitting topping bids. Plaintiffs also want to know whether Citigroup, financial adviser to Analogic for the deal, had any prior relationship with Altaris, and might therefore have been biased towards Altaris's bid. It is unlikely that the suit will manage to kybosh the acquisition – the deal already has the FTC's blessing and with $1bn on the table, Altaris and Analogic will fight hard to close it.

Novartis sweeps out the old for a new start

16 May, 2018

A sword has been duly fallen on, and Novartis will hope that the retirement of its general counsel, Felix Ehrat, will draw a line under the awkward revelations of the $1.2m paid to Michael Cohen, President Trump's personal lawyer and some-time pharma consultant. The fact that Mr Ehrat is unusually (in this day-and-age) taking "personal responsibility" should go a long way towards stopping the damage travelling higher up the food chain. Novartis needed to bring a swift conclusion to this debacle, which has dragged it into the US special counsel's investigation into Russian interference in the US presidential election. Aside from the embarrassment and negative PR, the affair was becoming a major distraction, with Novartis's chief executive, Vas Narasimhan, earlier this week calling 5,000 of his managers to discuss how the company could regain public trust. What will help Mr Narasimhan is that the deal took place under the watch of its previous chief exec, Joe Jimenez, though this was obviously not the start he was hoping for. In the few months he has been in charge Mr Narasimhan has set out a vision for Novartis, striving to reverse some of the public suspicion of big pharma. While some of this work will have been damaged, by saying goodbye to Mr Ehrat and replacing him with Shannon Thyme Klinger, the former chief ethics, risk and compliance officer, Mr Narasimhan is sending a clear signal about Novartis's future business dealings.

Cure is not a dirty word for Novo Nordisk

16 May, 2018

Has Novo Nordisk learned nothing from Gilead, which has been punished by investors and criticised by certain sellside analysts for curing hepatitis C? Apparently not, if a proud press release from the Danish company today is anything to go by, outlining notable progress in its efforts to cure type 1 diabetes. Novo said it had achieved preclinical proof of concept in research focusing on the differentiation of pluripotent stem cells into insulin-producing beta cells, and that it had made significant progress in developing an encapsulation device to protect transplanted beta cells from a patient's own immune system. The technology could move into human testing in the next couple of years; Novo also said it would increase its commitment to stem cell-based therapies, in type 1 diabetes and other chronic diseases, and said it would seek partnerships in these areas. Of course curing type 1 diabetes would have little impact on type 2 diabetes, which is a huge growth market for a large proportion of Novo's medicines. And if a cure is ever found the Danish company would obviously prefer to be involved. But the announcement suggests that Novo is preparing to put serious money into stem cell research – given the gene therapy revolution that is already under way it is surely time for investors and analysts to stop thinking about cures in the pejorative.

Phase II awaits for XEN1101, but Xenon's been here before

15 May, 2018

Xenon has chipped away at the fringes of biotech development for nearly two decades, with its main successes being licensing deals – it sold to the eventual Pfizer target Warner-Lambert intellectual property relating to high-density lipoprotein. But never before has one of its projects progressed beyond phase II. Investors this morning are betting that the epilepsy candidate XEN1101 might be different after data in just 42 healthy

volunteers – shares have risen 5% in early trading. The main focus appears to be a transcranial magnetic stimulation sub-study among eight healthy enrollees. Xenon says this analysis showed that patients taking a 20mg once-daily dose of its Kv7.2 potassium channel modulator showed similar resting motor threshold, a measure of trans-synaptic excitability, as those taking a 400mg dose of the now-withdrawn Potiga, which had a similar mechanism of action, in a study published in 2016. The main part of the phase I dosing study, meanwhile, indicated that XEN1101 did not have Potiga's adverse event profile, which included urinary retention and retinal pigmentation that prompted concerns about vision loss. Xenon expects a phase II study to begin later this year. XEN1101 appears to be in the lead in development of potassium channel modulators for epilepsy – only the preclincial KCNQ2 Programme from Knopp Biosciences appears to be being tested in the disorder.

Selected potassium channel modulators in clinical development

	Product	Pharmacological Class	Company	Therapeutic Subcategory
Phase II	AUT00063	Kv3 potassium channel modulator	Autifony Therapeutics	Ear/Otic preparations
Phase I	XEN1101	Kv7.2 potassium channel modulator	Xenon Pharmaceuticals	Anti-epileptics
	AUT00206	Kv3 potassium channel modulator	Autifony Therapeutics/Boehringer Ingelheim	Anti-psychotics
	Dalazatide	Kv1.3 potassium channel blocker	Aimid/KPI Therapeutics	Immunosuppressants
Pre-clinical	KCNQ2 Program	Kv7 potassium channel modulator	Knopp Biosciences	Other CNS drugs
	KPI-150	Kv1.3 potassium channel blocker	KPI Therapeutics	Other dermatologicals
	KPI-190	Kv1.3 potassium channel blocker	KPI Therapeutics	Eye/Ophthalmic preparations
	Anuroctoxin Research Program	Kv1.3 potassium channel blocker	University of Szeged	Immunosuppressants
	LifeArc-TetraGenetics Research Project	Anti-Kv1.3 potassium channel MAb	LifeArc	Anti-diabetics
	SVN-001	Anti-Kv1.3 potassium channel MAb	Eloxx Pharmaceuticals	Immunosuppressants

Source: EvaluatePharma

Cellcentric hopes to succeed where Tokai failed

15 May, 2018

Tokai Pharmaceuticals' shot at prostate cancer not amenable to treatment with anti-androgens crashed and burned, but others have not given up hope. Today Cellcentric, a private UK group, raised $26m to start clinical trials of CCS1477, a small molecule with a novel epigenetic approach to this problem, inhibiting the histone acetyl transferase proteins p300 and CBP. This, the company says, reduces expression of the androgen receptor as well as its splice variants. There is some similarity here with Tokai's galeterone, which was said to work in patients with the AR-V7 splice variant, but whose pivotal trial failed. There is an important difference between Cellcentric and Tokai: the former wants to target patients who have progressed on Zytiga, Xtandi or Erleada, while the latter had screened specifically for AR-V7-positive subjects who had not necessarily failed on these anti-androgens. Cellcentric says relapsed patients have increased expression of splice variants, as well as full-length and mutated androgen receptors, all of which might be inhibited by CCS1477. As Tokai found, the mechanism by which splice variants develop is highly complicated and poorly understood, so Cellcentric's phase I trial will be followed with interest.

Beam shines light on new Crispr tech

15 May, 2018

Professor Feng Zhang has a new company in the shape of Beam Therapeutics, whose investors will no doubt hope that the Crispr pioneer can pull off the same trick twice. Professor Zhang of the Broad Institute was famously involved in a dispute about who invented Crispr, and is already a co-founder of the public Crispr company Editas, which now has an equity stake in Beam. This is not the only thing the companies have in common: one investor in Beam's $87m series A round is F-Prime Capital, which was also involved in early funding of Editas and Intellia Therapeutics, two of the three public Crispr groups. Perhaps F-Prime believes that Beam can follow its fellows onto the stock markets. But Beam's flagship base-editing technology – licensed from Harvard University and the Broad Institute, and sublicensed from Editas – still has a long way to go. Unlike other Crispr companies Beam aims to edit one base within the genome without cutting the DNA or RNA; the edited molecule could be used to treat diseases caused by point mutations. There is clearly plenty of private money for a new kid on the Crispr block, but this will not make development timelines any shorter.

Public Crispr companies

Company	IPO date	Amount raised	IPO offering price per share	Current share price	Market cap	Private fundraising	Private investors
Editas Medicine	Feb 2016	$94m	$16	$36	$3.6bn	$165m series A & B	Alexandria Real Estate Equities, Casdin Capital, Cowen And Company, Deerfield Management, EcoR1 Capital Fund, Flagship Ventures, F-Prime Capital, Google Ventures, Jennison Associates, Khosla Ventures, Omega Fund, Partners Innovation Fund, Polaris Ventures, T. Rowe Price, Third Rock Ventures, Viking Global Investors
Intellia Therapeutics	May 2016	$108m	$18	$25	$1bn	$85m series A & B	Atlas Venture, EcoR1 Capital Fund, Foresite Capital, F-Prime Capital, Janus Capital Group, OrbiMed Advisors, Novartis, Sectoral Asset Management
Crispr Therapeutics	Oct 2016	$56m	$14	$57	$2.7bn	$162m series A & B and PIPE	Abingworth, Bayer Global Investments, Celgene, Franklin Templeton, New Enterprise Associates, New Leaf Venture Partners, SR One, Versant Ventures, Wellington Management

Source: EvaluatePharma

Lilly shows its hand twice

14 May, 2018

Some in biopharma continue to argue over whether assets are still overpriced, but Lilly seems to have no such qualms. The group's acquisition today of the virtually unknown private start-up Aurka Pharma came less than a week after it shelled out $1.6bn to buy Armo Biosciences. Today's deal is far smaller, valued at $110m up front, but it does illustrate another quiet industry trend: the increasing importance of small-molecule anticancer agents. Aurka's lead is AK-01, an Aurora kinase inhibitor. Thanks to groups like Blueprint Medicines kinase inhibition is enjoying a second lease of life in the face of the onslaught of immuno-oncology. However, Lilly's Aurka buyout is an embarrassing U-turn: AK-01 had actually been discovered at Lilly, but the group

deemed it non-core and sold it in 2016 to TVM Capital Life Science, which went on to found Aurka to develop the asset.

Selected aurora kinase inhibitors

Project	Company	Mechanism of action
Phase II		
ENMD-2076	Casi Pharmaceuticals	Aurora kinase A inhibitor
Ilorasertib (ABT-348)	Abbvie	Aurora kinase inhibitor
Alisertib	Takeda	Aurora kinase A inhibitor
AZD2811	Pfizer/Astrazeneca	Aurora kinase B inhibitor
GSK1070916	Glaxosmithkline	Aurora kinase inhibitor
Danusertib	Nerviano Medical Sciences	Aurora kinase inhibitor
NMI-900	Nemucore Medical Innovations	Aurora kinase B inhibitor
AK-01	Lilly/Aurka	Aurora kinase A inhibitor
Phase I		
TAS-119	Otsuka Holdings	Aurora kinase A inhibitor
Chiauranib	Shenzhen Chipscreen Biosciences	Aurora kinase B inhibitor & VEGFR inhibitor
Preclinical		
Aurora+FLT3 Kinase Program	Sareum	Aurora kinase inhibitor; FMS-like tyrosine kinase 3 inhibitor
AL8326	Advenchen Laboratories	Aurora kinase B inhibitor FGFR inhibitor & VEGFR inhibitor
Aurora Kinase Inhibitor Research Program	Vichem Chemie	Aurora kinase inhibitor
KIN 4064	Kinentia Biosciences	Aurora kinase B inhibitor

Source: EvaluatePharma.

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