Evaluate Vantage

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Snippet roundup: Cyclacel's data dredge and Bristol's activist investor

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

This week, February 20-24, 2017, we had thoughts on the following: Cyclacel dredges its way out; Bristol fails to contain investor disquiet; analgesic causes pain for Trevena; Sarepta's voucher sale confirms the peak is past; Insulet looks to Horizon, but Medtronic already there; Torax follows medtech script perfectly with takeout by J&J.

These snippets were previously published daily via twitter.

Cyclacel dredges its way out

February 23, 2017

When you find yourself several metres beneath the bottom of the lake it might be time to stop dredging. The Seamless study of Cyclacel's acute myeloid leukaemia project sapacitabine failed a futility analysis in late 2014, and it was vanishingly unlikely that sifting the data would yield anything useful. So it has proved, with the company admitting that no improvement in overall survival was seen with alternating cycles of sapacitabine and decitabine versus continuous decitabine. Seemingly undeterred, Cyclacel stated that an improvement in OS was seen in a subgroup of patients with low baseline peripheral white blood cell count, with the Seamless trial investigator saying that additional analysis of subgroups was warranted. The group's investors are not keen on waiting for more subgroup studies: shares closed down 25% on Thursday. This means that any investors still holding Cyclacel shares having bought at the split-adjusted IPO price of $672 have lost 99.4% of their money 13 years later.

Selected phase III AML trials

Project	Company	Patients	Design	Trial ID	Data
Sapacitabine	Cyclacel	485	+/- decitabine	NCT01303796	Fail
Quizartinib	Daiichi Sankyo	326	vs salvage chemo	NCT02039726	May 17
Guadecitabine	Otsuka	800	vs TC	NCT02348489	December 17
Idasanutlin	Roche	440	+/- cytarabine	NCT02545283	April 18
Iomab-B	Actinium	150	vs conventional care	NCT02665065	April 18
Oral Vidaza	Celgene	460	+/- BSC	NCT01757535	August 18
Treosulfan	medac	960	vs busulfan RIC	NCT00822393	January 19
Enasidenib	Celgene/Agios	280	vs convention therapy	NCT02577406	April 19
Gilteritinib	Astellas	540	+/- azacitidine	NCT02752035	July 19
Vadastuximab talirine	Seattle Genetics	500	+/- HMA	NCT02785900	September 19
Quizartinib	Daiichi Sankyo	536	+/- induction SoC	NCT02668653	January 20
Gilteritinib	Astellas	369	vs salvage chemo	NCT02421939	March 20

Bristol fails to contain investor disquiet

February 22, 2017

Just when Bristol-Myers Squibb thought it had neutralised one threat, another emerges. Yesterday's non-executive appointments, temporarily increasing its board from 11 to 14 directors, and $2bn stock buyback came after discussions with Jana Partners, an activist investor that had taken a position in the struggling company. However, on the same day a much more notorious activist – Carl Icahn – was reported to have bought a Bristol stake. Judging by Mr Icahn's dealings with companies like Amylin and Imclone, his presence on the investor register tends to preface management upheaval and/or a trade sale to release shareholder value, and sure enough Bristol spiked 2% on the news yesterday. It is easy to see Bristol as undervalued: its stock is hugely dependent on Opdivo, which is down but by no means out after a stumble in first-line lung cancer that could still be down to luck of study design (*For Bristol Opdivo gives and it takes away, February 15, 2017*). The company's lack of a poison pill makes it takeover-friendly, but for a company like Pfizer to pull the trigger would require bullish views on Opdivo, the pipeline, and the US political approach to cost cutting. None of these bets is easy to make.

Analgesic causes pain for Trevena

February 21, 2017

Oliceridine is good, but not good enough. Trevena's intravenous opioid met its primary endpoints in two phase III trials, beating placebo on analgesic effect in patients with moderate to severe acute pain following bunionectomy or abdominoplasty. And the two higher doses – three were tested in each trial – gave comparable pain reduction to morphine. But investors had expected more: early data had suggested that oliceridine might be able to do all this with a better side-effect profile than morphine, and here it disappointed: side-effects were, like efficacy, comparable to morphine. Trevena intends to submit for approval once results from a third trial come in, and might well get it thanks to the hit on the primaries coupled with oliceridine's breakthrough status. But there is little case to be made for doctors to favour the drug over morphine, and its limited market potential forced Trevena's shares down 40% yesterday.

Endpoint	Doses achieving significance
Apollo-1: bunionectomy, oliceridine 0.1mg, 0.35mg and 0.5mg	
Analgesic efficacy vs placebo, as measured by responder rate	All
Efficacy vs morphine at 48 hours, based on responder rate	0.35mg and 0.5mg
Respiratory safety burden vs morphine	0.1mg
Prevalence of oxygen desaturation vs morphine	0.1mg
Prevalence of supplemental oxygen use vs morphine	0.1mg
Rates of antiemetic use vs morphine	All
Prevalence of nausea and vomiting vs morphine	0.1mg
Apollo-2: abdominoplasty, oliceridine 0.1mg, 0.35mg and 0.5mg	
Analgesic efficacy vs placebo, as measured by responder rate	All
Efficacy vs morphine at 24 hours, based on responder rate	0.35mg and 0.5mg
Respiratory safety burden vs morphine	0.1mg
Prevalence of oxygen desaturation vs morphine	0.1mg
Prevalence of supplemental oxygen use vs morphine	0.1mg
Rates of antiemetic use vs morphine	0.1mg
Prevalence of nausea and vomiting vs morphine	0.1mg
Prevalence of vomiting vs morphine	0.35mg

Sarepta's voucher sale confirms the peak is past

February 21, 2017

Estimates of up to $350m for Sarepta's priority review voucher, awarded on approval of Exondys 51, have been proved vastly overblown. The $125m sale price, paid by Gilead, marks the lowest for one of these tickets to regulatory rapidity in two years. Optimists were ignoring clear signs that the price tag of these vouchers was set to decline: Gilead is thought to have paid around $200m for Paxvax's last year, while their scarcity value has presumably been dented by the extension of the paediatric programme, meaning the FDA can issue more in the coming months. The sale also confirms Gilead as an enthusiastic purchaser. The antiviral giant has now spent $450m bagging these coupons, seemingly seeing more value here than in the M&A targets it is under so much pressure to acquire.

The fate of disclosed priority review vouchers

Date sold	Price	Date issued	Voucher type	Issued company	Action
–	–	Apr 2009	Tropical disease	Novartis	Redeemed by Novartis in BLA for Ilaris (gout)
Jul 2014	$67.5m	Feb 2014	Rare paediatric	Biomarin	Sold to Sanofi & Regeneron; redeemed for Praluent (high cholesterol)
Sep 2014	Not disclosed	Sep 2015	Rare paediatric	Wellstat	Transferred to AstraZeneca in licensing deal
Nov 2014	$125m	Mar 2014	Tropical disease	Knight	Sold to Gilead; redeemed for Odefsey (HIV)
May 2015	$245m	Mar 2015	Rare paediatric	Asklepion	Sold to Sanofi; redeemed for LixiLan (diabetes)
Aug 2015	$350m	Mar 2015	Rare paediatric	United	Sold to Abbvie
Q2 2016*	~$200m**	Jun 2016	Tropical disease	Paxvax	Likely sold to Gilead*
Feb 2017	$125m	Sep 2016	Rare paediatric	Sarepta	Sold to Gilead
–	–	Dec 2012	Tropical disease	J&J	None
–	–	Oct 2015	Rare paediatric	Alexion	None***
–	–	Dec 2015	Rare paediatric	Alexion	None***
–	–	Dec 2016	Rare paediatric	Biogen	None
–	–	Feb 2017	Rare paediatric	Marathon	None

*Notes: *Gilead revealed purchase of undisclosed PRV in Q2 statement; **based on Gilead disclosure of $624m increase in R&D spend, less $400m Nimbus purchase and undisclosed clinical trial progression; ***assumed, as Alexion, a listed entity, would likely have had to disclose transfer.*

Insulet looks to Horizon, but Medtronic already there

February 20, 2017

Shares in Insulet opened 4% higher today after positive data from the first feasibility study of its hybrid closed-loop glucose delivery system, a step on the way to a true artificial pancreas. In the 24-patient study of adults with type 1 diabetes the Omnipod Horizon, which uses a proprietary algorithm to measure glucose levels constantly and deliver insulin, showed significant reductions from baseline in the time patients spent in a hypoglycaemic state. Nearly 70% of patients remained within the target blood glucose range during the 36-hour trial, and more importantly 90% of patients stayed within a safe range overnight. Despite good data for Horizon, Insulet is lagging others in the field. A readout from Cellnovo's 240-patient trial is expected this year,

and Medtronic's Minimed 670G was approved in 2016. Insulet is not forecast to launch its Horizon product before 2019, so it will have a lot of catching up to do.

Selected artificial pancreas programmes

Company	Product	Status
Medtronic	MiniMed 530G plus Enlite sensor	Approved in US September 26, 2013
Medtronic	MiniMed 630G plus Enlite sensor	Approved in US August 10, 2016
Medtronic	MiniMed 670G plus Enlite 3CGM	Approved in US September 29, 2016
Medtronic	Next-generation artificial pancreas system	100-patient US and European trial (NCT03040414) due to start late 2017; data expected late 2019
Tandem Diabetes/ Dexcom/TypeZero	Tandem's t:slim pump plus Dexcom CGM, incorporating TypeZero's algorithms	Currently in 240-patient international trial (NCT02985866); data expected early 2018
Cellnovo/academic and government researchers	Diabeloop	Currently in 60-patient European trial (NCT02987556); data expected late 2017
Insulet	OmniPod plus DexCom CGM	US feasibility study (NCT02897557) complete

Source: clinicaltrials.gov; company websites

Torax follows medtech script perfectly with takeout by J&J

February 20, 2017

Form company, check. Raise money, check. Get product approval, check. Get bought, check. The private company Torax Medical on Friday said it had realised the medtech dream with a signed takeover agreement from Johnson & Johnson's Ethicon division. The takeout from the US pharma giant's surgery arm comes after the usual validation of Torax's business model in the form of approvals for its lead products. The Linx oesophegal reflux management system for GERD was approved in 2012, while the Fenix Continence Restoration system got the nod from regulators in 2016. Both products rely on interlinked titanium beads with magnetic cores to help keep the oesophagus or anus closed stopping either acid reflux or faecal incontinence. Ethicon's chief reason for the takeout, which did not have disclosed terms, is the lure of a safe and effective minimally invasive alternative to current surgical procedures. For Torax, whose last $25m series E funding round was led by J&J Innovation, this was the culmination of a successful working relationship with a group capable of accelerating its sales.

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