Evaluate Vantage

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Snippet roundup: The good times roll for Moderna, but Mallinckrodt and Smith & Nephew flag

Edwin Elmhirst

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

This week, April 30-May 4, 2018, we had thoughts on the following: Merck & Co throws some more cash at Moderna; Mallinckrodt: Acthar and not much else; S&N chief departs with a profit warning; Achaogen haemorrhages value over blood infection doubts; J&J's Benevir buy cements oncolytic virus trend; Edwards needs more heart to repair growth prospects; Pfizer sends mixed messages on M&A; ozanimod metabolite fears spark another Celgene selloff; Icer draft says new psoriasis treatments are cost-effective or very close.

These snippets were previously published daily via twitter.

Merck & Co throws some more cash at Moderna

May 4, 2018

Biotechs should always raise money not when they need to but when they can. A case in point is Moderna Therapeutics: barely three months after cementing its unicorn status by raising $500m at a $7bn valuation, the private mRNA-focused group has completed a $125m series H round courtesy of Merck & Co. This latest raise was driven by an expansion of the groups' 2016 collaboration to develop personalised mRNA-based cancer vaccines, an effort that resulted in mRNA-4157 entering the phase I Keynote-603 trial in combination with Keytruda last year. The expanded effort encompasses mRNA-5671, Moderna's off-the-shelf vaccine against the highly undruggable KRAS mutation. The recent failure of Merck and Incyte's IDO approach has hastened other immuno-oncology combinations, including with IL-2 and oncolytic viruses. But the history of cancer vaccine development is littered with failures, and the idea that simply stimulating endogenous T-cell receptors is enough lacks a scientific basis, though perhaps combinations hold the key. At least Moderna does not need to worry about running out of money: with the latest raise it now has over $1.5bn in the bank.

Mallinckrodt: Acthar and not much else

May 4, 2018

The dismissal of Mallinckrodt's severe jaundice candidate Stanate by an FDA adcom yesterday pushed the group's stock down 7% and leaves it even more dependent on sales of its multiple sclerosis exacerbations therapy Acthar than it already was. The verdict was damning: panellists voted that the drug had not been proven effective, and that it had not been proven safe in either the long or short term. The vote on the risk-benefit of Stanate's approval went 3-21 against. Even accounting for the FDA's recent blasé attitude to dubious drugs it is hard to see this one getting waved through. Though Stanate's forecast sales are, at $98m in 2024, hardly enormous, losing them would boost Mallinckrodt's reliance on Acthar; revenue from the drug will make up 62% of the group's total sales in 2021 and 56% in 2024, if Stanate is not approved, according to the sellside. If Stanate is rejected Mallinckrodt's best pipeline hope will be CPP-1X/sulindac, in phase III development for familial adenomatous polyposis, a condition that leads to colon cancer. The cytostatic came via the $1.2bn acquisition of Sucampo Pharmaceuticals in December and is forecast to sell $65m in 2024.

Mallinckrodt's ongoing dependency on Acthar

	2017	2018e	2019e	2020e	2021e	2022e	2023e	2024e
H.P. Acthar Gel sales ($bn)	1.20	1.09	1.11	1.11	1.12	1.10	1.08	1.07
Acthar sales as % of total	38%	55%	56%	55%	60%	59%	56%	53%
Acthar sales as % of total minus Stanate	38%	55%	56%	56%	62%	61%	58%	56%

Source: EvaluatePharma

S&N chief departs with a profit warning

May 3, 2018

"I wish I could have left the company with a better quarter than this one," Olivier Bohuon, chief executive of

Smith & Nephew, said on the group's first-quarter conference call this morning. He is probably not the only one feeling that way. Revenues of $1.2bn, flat from the year before on an underlying basis, missed consensus expectations and prompted the company to issue a profit warning. S&N reduced revenue guidance to 2-3% for underlying growth for 2018, down from 3-4% previously, and said its profit margin would be flat year on year. The company's London and New York-listed shares opened down 7% and 6%, respectively. Mr Bohuon stated on the call that he had no regrets in deciding not to sell off parts of S&N – both the hips and knees and the wound care units were mooted as missed divestment opportunities – but the dismal quarterly performance will surely lead to renewed calls for streamlining, not least from the activist investor Elliott Advisors. These will be decisions for S&N's new chief, Namal Nawana, who takes over the corner office on Monday.

Achaogen haemorrhages value over blood infection doubts

May 3, 2018

It looks like Achaogen's antibiotic plazomicin is heading for approval in complicated urinary tract infections. But this was no consolation to investors who were also hoping for a green light in the more lucrative indication of bloodstream infections caused by carbapenem-resistant enterobacteriaceae (CRE). A US FDA advisory panel voted in favour of approval in the former, but not in the latter, sending the company's share price down 26% in premarket trading this morning. The sellside tried to fight the fire, with Leerink and Stifel analysts suggesting that even if not approved specifically for CRE plazomicin might still be used off label in this indication. They used the example of Allergan's Avycaz, which brought in around $60m in 2017, the majority from off-label use in CRE. Still, Achaogen investors face a nervous wait before plazomicin's June 25 PDUFA date, and will hope for at least some mention of CRE in its label. There are also fears that the adcom vote could put other companies off the underserved antibiotic space – plazomicin was the first antibiotic to be reviewed under the limited-population antibacterial drug (LPAD) pathway. This scheme was supposed to ease antibiotic development, partly by allowing smaller studies – ironically the small size of the Care trial was a sticking point with Achaogen's CRE application.

Plazomicin's problem...

	2024e sales ($m)
Urinary tract infection sales	203
Total sales	563
Urinary tract infection sales as % of total	36%

Source: EvaluatePharma

J&J's Benevir buy cements oncolytic virus trend

May 2, 2018

Investors had waited years for an oncolytic virus deal, and then two came along in quick succession. Johnson & Johnson's purchase today of the preclinical-stage company Benevir, a couple of months after Merck & Co shelled out $394m for Viralytics, confirms that the technology is back in vogue despite previous clinical and commercial failures. The J&J-Benevir deal, worth $140m up front and up to $900m in milestones, represents an impressive return for the latter's investors, including HC2 Holdings, which have put just $6m into the company since its inception in 2011. It is unclear whether J&J is in the best position to pull off this bet, however. As part of its plan to develop Benevir's T-Stealth oncolytic viruses – which the company claims are the first to resist both innate and adaptive immunity – J&J will test them both alone and in combination with immunotherapies. But unlike Merck, which will combine Viralytics' Cavatak with its PD-1 inhibitor, Keytruda, J&J is not exactly a heavy hitter in immuno-oncology. On its earnings call yesterday Merck highlighted oncolytic viruses as an area of focus in light of the recent IDO/PD-1 combo failure. J&J will need something special to compete.

Oncolytic virus buyouts of the last decade

Buyer	Acquired company (project)	Deal value ($m)	Upfront portion ($m)
2018			
Johnson & Johnson	Benevir (T-stealth platform)	1,400	140
Merck & Co	Viralytics (Cavatak)	394	
2017			
Sorrento Therapeutics	Virtuu (Seprehvir)	25	5
2014			
SillaJen Biotherapeutics	Jennerex (Pexa-Vec)	150	-
2011			
Amgen	Biovex (Oncovex)	1,000	425

Source: EvaluatePharma

Edwards needs more heart to repair growth prospects

May 2, 2018

Edwards Lifesciences' efforts to move into new spaces are paying off, with European approval for its Cardioband heart repair device in its second indication, tricuspid regurgitation. But, with the company's core transcatheter aortic valve franchise disappointing in the first quarter, Edwards needs its new products to pick up the pace. So far the signs are not great: Edwards posted first-quarter sales of less than $1m for its transcatheter mitral repair offering, which includes European Cardioband revenues in its first indication, mitral regurgitation. And Leerink analysts forecast that the product will reach $35m by 2021 – dwarfed by the $340m up front that Edwards paid for its developer, Valtech Cardio, in 2016, and less than the $50m that Edwards

must pay Valtech investors on receipt of the tricuspid CE mark. Getting US approval could be the key to growing Cardioband sales, but here the project is well behind Abbott's rival Mitraclip device, which has been approved for mitral regurgitation since 2013. In mitral disease, Cardioband is in a US pivotal trial, Active, which is set to complete in 2020. Meanwhile, in triscuspid disease Edwards is not yet off the blocks in the US; during its first-quarter earnings call its chief executive, Michael Mussallem, said it was activating sites for an early US feasibility study.

Pfizer sends mixed messages on M&A

May 1, 2018

Ian Read has been with Pfizer since the 1970s, so he surely knows that the company he has headed for more than seven years has been built on mega-mergers. So it seems to have caused some consternation today when the message from executives during the first-quarter earnings call was all about the Pfizer pipeline, with a resulting 5% slump in shares at midday. Mr Read told investors that he did not see the need to do a "transformative" deal and that he hoped his legacy would be an "extremely robust pipeline", messages that are not normally associated with the acquisitive pharma giant. Perhaps after his bullish comments three months ago about being in the "forefront" of the next mega-merger wave and Pfizer's "core competency" at absorbing big companies, talking down M&A was not want investors wanted to hear. With slowing drug sales, and a disappointing quarter for big growth driver Ibrance, investors may want to hear more about how Pfizer hopes to regain some momentum on topline sales. In addition, some might have been hoping that the Takeda bid on Shire might serve as a trigger for more big moves. Of course, it could just be that Mr Read is talking down M&A as a way to suppress valuations – however, the mixed messages do not seem to be serving Pfizer's own valuation very well.

Mind the innovation gap? Pfizer's most valuable pipeline projects

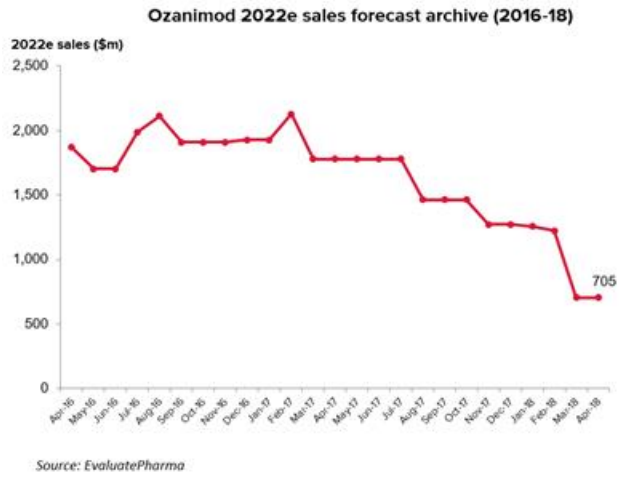
Product	Type	Today's NPV ($bn)
PF-05280586	Biosimilar Rituxan	3.09
PF-05280014	Biosimilar Herceptin	2.82
PF-06439535	Biosimilar Avastin	2.82
Tanezumab	Anti-NGF Mab (pain)	2.46
PF-06410293	Biosimilar Humira	1.78
Talazoparib	Parp inhibitor (ovarian/breast cancer)	1.67
Dacomitinib	HER/ErbB inhibitor (lung cancer)	1.20
PF-06425090	Clostridium difficile vaccine	0.71
Lorlatinib	ALK & ROS1 kinase inhibitor (lung cancer)	0.55
Glasdegib	SMO inhibitor (leukaemia)	0.34
	Total R&D pipeline NPV	**18.85**
	Total Marketed NPV	**186.32**
	Pfizer NPV	**205.17**
	Market cap	**207.67**

Source: EvaluatePharma

Ozanimod metabolite fears spark another Celgene selloff

May 1, 2018

Celgene investors have got used to disappointments over the past 12 months, and now they have something else to worry about. On May 4 the group is due to report its first-quarter financials, at which it has promised to give an update on the status of ozanimod, the potential multiple sclerosis blockbuster that was spectacularly knocked back with a US refusal-to-file letter in February. The signs are not good, and Celgene's market cap lost $3bn yesterday. This was triggered by an email the company sent to the sellside last week, highlighting an American Academy of Neurology presentation covering the ozanimod metabolite CC112273, now seen as the reason for the US setback. If this active metabolite has been insufficiently characterised, the bear thesis goes, rectifying this problem could necessitate another one to two years of preclinical study. Umer Raffat, an analyst from Evercore ISI who had pinned the blame on a metabolite as soon as the FDA rejection was announced, reckons on a much shorter delay, saying that a two-year rodent carcinogenicity study might be done post approval, and could even be under way already. All will be revealed on Friday.



Source: EvaluatePharma

Icer draft says new psoriasis treatments are cost-effective or very close

April 30, 2018

The new psoriasis agents Siliq and Tremfya represent cost-effective options for treating moderate to severe plaque psoriasis when compared against non-targeted agents like corticosteroids and methotrexate, according to an independent US evaluator. In a draft update to its 2016 report that appraised Lilly's Taltz, Novartis's Cosentyx and Johnson & Johnson's Stelara in psoriasis, the Institute for Clinical and Economic Review has determined that Valeant's Siliq costs $120,750 per quality adjusted life year (QALY) gained over non-targeted therapy, and J&J's Tremfya $146,638. The report also put a cost-per-QALY number of $120,158 on UCB's rheumatoid arthritis drug Cimzia, which is due an FDA decision later this month in psoriasis. Only one agent exceeds Icer's $150,000 per QALY threshold: Johnson & Johnson's Stelara. The report also estimated how much could be charged for Abbvie's risankizumab, which has been filed, and Sun and Merck & Co's recently approved Ilumya while allowing them to meet the $150,000/QALY threshold: $3,342 per monthly dose for the former and $9,253 per quarterly dose for the latter.

Icer's score on psoriasis drugs

First-line Treatment	Cost / QALY	Cost / month in PASI 90+**	Cost / month in PASI 75+ **
Humira	$149,385	$4,200	$3,010
Otezla	$122,882	$3,826	$2,603
Siliq*	$120,750	$2,932	$2,423
Cimzia*	$120,158	$3,369	$2,415
Enbrel	$156,863	$4,556	$3,232
Tremfya*	$146,638	$3,603	$2,940
Remicade	$119,572	$2,964	$2,471
Taltz	$130,695	$3,056	$2,634
Cosentyx	$133,527	$3,295	$2,677
Stelara	$152,678	$4,091	$3,064

*Source: Icer *New estimate **Psoriasis Area Severity Index reductions of 90% and 75%*

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