Evaluate Vantage

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Snippet roundup: Novartis's allogeneic CAR-T drive and Astra's IL-4 interest

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

This week, May 1 to 5, 2017, we had thoughts on the following: Outset sets out for market with $77m; Livanova gets into mitral; Astra signals interest in high risk asthma target; Novartis gives Cellectis and Oxford Biomedica something to worry about; Carmat can restart trial but launch delayed; Abivax hits in phase II; Aeterna and Neurotrope join the 60% club.

These snippets were previously published daily via twitter.

Outset sets out for market with $77m

May 4, 2017

Outset Medical previously distinguished itself by raising the ninth-largest medtech venture funding round of 2015. It has now secured another impressive haul, closing a $77m series C that is the third-biggest round so far this year. Proceeds will be used to aid the launch of its haemodialysis system, Tablo. Tablo is CE-marked and FDA-approved for use in dialysis clinics, hospitals and other facilities, but Outset is conducting a US trial to expand its label to include home use. According to Clinicaltrials.gov the study, in 50 patients, will compare treatment with the device when administered by staff in a healthcare centre with its use by patients at home. The study is due to conclude in December 2018. Tablo connects directly to the tap water supply, purifying it and generating dialysis fluid as the patient is dialysing. Outset says this can reduce costs in hospitals and other care facilities as well as enabling the reach into the home setting.

Outset's venture funding

Financing Date	Round	Investment ($m)	Investor Name
May 4, 2017	Series C	76.5	Fidelity Management & Research, Partner Fund Management, Warburg Pincus, Perceptive Advisors, The Vertical Group and funds advised by T. Rowe Price Associates
June 9, 2015	Undisclosed	51.0	CRG, F-Prime Capital, Partner Fund Management, Perceptive Life Sciences Fund, Vertical Group, Warburg Pincus
February 24, 2011	Undisclosed	5.0	Undisclosed
February 26, 2010	Undisclosed	4.5	Undisclosed
	Total	137.0	

Source: EvaluateMedTech

Livanova gets into mitral

May 4, 2017

In paying $18m for the 51% of Caisson Interventional that it didn't already own, Livanova has become the latest group to buy its way into the transcatheter mitral valve space. Livanova, which first invested in Caisson in 2012, will pay an additional $54m to the group's owners when milestones are hit, and will also forgive $6m of debt. Caisson's valve began a 20-patient feasibility study, Prelude, in the US last year which was due to complete in December, but no data have yet emerged. Nonetheless Livanova says the device will be the "cornerstone" of its planned entry into the mitral space, complementing its current heart valve portfolio. Just as well; the UK's regulator the MHRA issued a warning yesterday over Livanova's surgically implanted Mitroflow LX aortic valves, stating that some devices – though probably less than 80 – carry an increased risk of early structural valve deterioration. Livanova intends to start a surveillance study of UK Mitroflow LX patients. Its shares closed up 3% yesterday, but that was likely on its first-quarter results: net income was $11.3m, compared with a loss of $40.4m a year earlier.

Livanova's cardiac business

Area	Segment	EvaluateMedTech Device Classification - L3	2016	2022	CAGR
Cardiopulmonary	Heart-lung machines	Cardiopulmonary bypass devices	182	254	6%
Cardiopulmonary	Oxygenators	Cardiopulmonary bypass devices	351	488	6%
Cardiopulmonary	Autotransfusion machines and devices	Autotransfusion apparatus	109	153	6%
Heart valve	Mechanical heart valves	Mechanical heart valves	74	96	4%
Heart valve	Tissue heart valves	Tissue heart valves	93	125	5%
Heart valve	Others	Cardiac prosthetic devices	19	23	3%
Total	*Cardiac Surgery*	*Unclassified*	*828*	*1,139*	5%

Source: EvaluateMedTech

Astra signals interest in high-risk asthma target

May 3, 2017

With its Pieris deal Astrazeneca has signalled keen interest in an asthma target that is grounded in considerable biological rationale, but which remains largely unexploited by the pharmaceutical industry. IL-4 is heavily involved in airway inflammation and activation of type 2 T helper cells (Th2 cells), an important disease driver in asthma. Efforts to utilise the target have largely come to nothing, although Sanofi and Regeneron's recently approved dermatitis antibody Dupixent hits both IL-4 and IL-13 – the cytokines have similar functions and both signal through the IL-4 receptor – and phase III results in asthma should read out later this year. PRS-060, the most advanced subject of Astra's attentions, inhibits the IL-4 receptor; the molecule is an anticalin, an engineered protein that Pieris describes as smaller than an antibody and offering the potential of inhaled delivery. Injected antibodies targeting IL-5 are already on the market in severe types of asthma, but with PRS-060 Astra must be hoping for a product that carries broader potential. A development pipeline littered with failures demonstrates that this is a high-risk area.

Hitting the IL-4 target in asthma

Active products	Company	Pharmacological Class	Comment
Dupixent	Sanofi/Regeneron	Anti-IL-4 & IL-13 MAb	P3 results due H2'17
PRS-060	Pieris Pharmaceuticals	IL-4 alpha receptor antagonist	P1 trial to start H2'17
BNZ-3	Bioniz Therapeutics	IL-4, IL-9 & IL-21 inhibitor	Pre-clinical
Potential products			
MEDI9314	AstraZeneca	Anti-IL-4 alpha MAb	P1 - targeted at atopic dermatitis
Notable abandoned clinical projects			
AIR645	Altair Therapeutics	IL-4 receptor alpha RNAi therapeutic	Abandoned in P2 around 2010
Pitrakinra	Aerovance	Anti-IL-4 & IL-13 MAb	Abandoned in P2 around 2010
AMG 317	Amgen	Anti-IL-4 & IL-13 MAb	Abandoned in P2 in 2009
Pascolizumab	GlaxoSmithKline	Anti-IL-4 MAb	Abandoned in P2 in 2003
Altrakincept	Immunex	IL-4 receptor antagonist	Abandoned in P2 in 2002
IL-4/ 13 Trap	Regeneron	Anti-IL-4 & IL-13 MAb	Abandoned in P1 in 2006
AVE-0309	Aventis	IL-4 receptor antagonist	Abandoned in P1 in 2003

Novartis gives Cellectis and Oxford Biomedica something to worry about

May 3, 2017

Novartis last year gave the impression that its cell therapy work was taking a back seat, but two early-stage deals struck yesterday suggest that it is not taking its foot off the gas. The Swiss firm's licence to a Celyad patent covering T cell receptor-deficient T cells could mark the beginning of an allogeneic CAR-T programme, and the technology is to be used with two undisclosed Novartis targets. Celyad and its rival Cellectis have been embroiled in an acrimonious battle over the patent involved, and Cellectis, the most advanced player in allogeneic CAR-T therapy, will now have Novartis to contend with. Novartis's second deal, with Bluebird Bio, is more curious, involving the US biotech group's knowhow in lentiviral vector technology. This is unusual because Novartis already has an alliance with Oxford Biomedica covering lentivirus manufacture – a vital part of the CAR-T production process. Perhaps Novartis is looking to do this itself, which would be very troubling for Oxford; on the other hand, global lentiviral capacity is extremely stretched, so perhaps the Swiss firm just wants a second source of vector or to secure its supply.

Disclosed allogeneic CAR-T approaches

Group	Genome-editing technology	Projects
Cellectis/Servier/Pfizer	Talen, via RNA electroporation	UCART19 in the clinic; preclinical pipeline
Novartis/Intellia/Penn	Crispr/Cas9, via RNA electroporation	Preclinical work on TCR, HLA & PD1 knockouts
Sangamo	Zinc-finger nuclease	Subject to grant of licence to NCI's fully human CD19-CAR
Kite/UCLA	None selected	None; licence to artificial thymic oranoid as T cell source
J&J/Transposagen	Piggybac footprint-free	None disclosed
Celyad/Novartis	None disclosed	None; US patent for TCR-deficient T cells
Shire/Precision Biosciences	Arcus nuclease	None disclosed
Ziopharm/MD Anderson	None disclosed*	Stem cell donor-derived CD19-directed CAR in clinical trials

*Note: *this group uses the Sleeping Beauty transposon/transposase to express the CAR, but since the project uses donor-derived T cells it is not a true, universal off-the-shelf approach.*

Carmat can restart trial but launch delayed

May 3, 2017

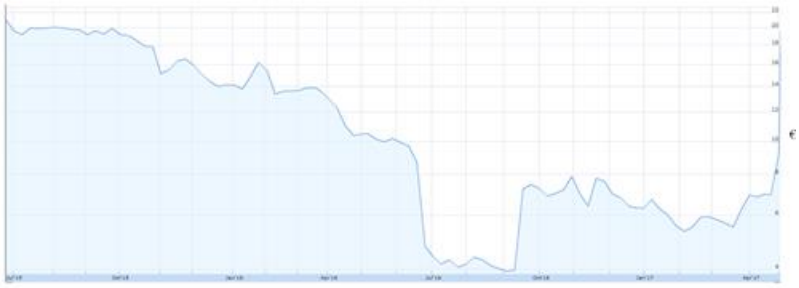
Carmat is clear to resume the CE mark trial of its artificial heart after the French regulatory authority ANSM said the group had met its conditions of safety and risk control. In early trading today its shares jumped 15% to €30.54 ($33.32), the highest since early December. The Advance HF trial had been halted after the first patient recruited into it died last October. Now Carmat will begin to enrol a further 19 patients with end-stage biventricular heart failure, and intends to expand the pivotal trial to countries outside France – but with a six-month survival endpoint it is hard to see this study concluding until spring 2018. Carmat said it would open a new production site by the end of this year to build the devices for the study, and to eventually meet manufacturing targets for commercial launch. Less than a year ago Carmat was confident of European launch in 2018; now analysts are not expecting the €150,000 product to reach market before 2020.

Abivax hits in phase II

May 2, 2017

After releasing promising phase II data, indicating that 28 days of ABX464 treatment can reduce viral reservoirs in HIV patients, Abivax says it now plans to initiate longer trials aimed at establishing the pill as a functional cure. This would represent a huge step forward in treatment – while HIV drugs now are able to control replication effectively, they cannot eliminate the virus from patients. In the small phase IIa study, ABX464 was added to patients' antiretroviral treatment for 28 days and then interrupted to measure viral

rebound. In 18 evaluable patients seven of 14 taking ABX464 were classified as responders – seeing reductions of 25% or more at the end of follow-up – with a mean reduction of 40% and a range of 27-67%. There were no responders among the four patients taking placebo. Abivax's share price more than doubled today to €19.70, which should allow the French group to raise money and top up cash reserves that stood at €23m at the end of 2016.



EPA: ABVX since float

Aeterna and Neurotrope join the 60% club

May 2, 2017

Two biotechs, two trial failures, two huge falls in value. Shares in Aeterna Zentaris collapsed 60% yesterday when the company said it was shelving its peptide-doxorubicin conjugate Zoptrex after it missed in a phase III study in endometrial cancer. The agent did not improve on doxorubicin alone, the standard of care, giving Aeterna little cause to pursue Zoptrex any further. Its hopes now rest on Macrilen, an adult growth hormone deficiency diagnostic agent, but consensus sales forecasts for Macrilen stand at just $18m in 2022, according to *EvaluatePharma*, to Zoptrex's pre-failure $143m. It was the ever-challenging indication of Alzheimer's disease that did for Neurotrope, meanwhile, whose stock fell 63% on the phase II failure of Bryostatin-1. Ambitiously, the company targeted moderate to severe disease with a trial testing two doses of Bryostatin-1 against placebo. It claims that the lower dose, 20µg, met the primary endpoint of improvement on the severe impairment battery (SIB) scale among patients who completed the trial – but gave a p value of <0.07, which is non-significant. Bryostatin-1 20µg missed in the modified intent-to-treat population. The company did not release data on the higher dose in the trial, 40µg, stoking fears that the failure was across the board.

Company	Agent	Trial	Endpoint	Result
Aeterna Zentaris	Zoptrex	Phase III - NCT01767155	Median OS	10.9 months vs 10.8 months with doxorubicin
Aeterna Zentaris	Zoptrex	Phase III - NCT01767155	Median PFS	Identical to doxorubicin
Neurotrope	Bryostatin-1 20µg (completers)	Phase II - NCT02431468	Mean change on the SIB scale	+1.5 vs -1.1 with placebo (p<0.07)
Neurotrope	Bryostatin-1 20µg (mITT)	Phase II - NCT02431469	Mean change on the SIB scale	+1.2 vs -0.8 with placebo (p<0.14)

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