Evaluate Vantage

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Snippet roundup: Approvals for Array and Dermira, but Achaogen falls short

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

This week, June 25-29, 2018, we had thoughts on the following: no sweat over Dermira's antiperspirant cloth; Novartis to spin off Alcon for half of what it paid; first approval for Array with more catalysts to come; Keryx gives Akebia new focus as vadadustat wait continues; Nippon Shinyaku takes on Sarepta but patent questions remain; Astra-Merck's Parp Lynparza pushes ahead in ovarian cancer; a hit and a miss for Achaogen; good things come in small packages for Glaukos; death stalls Sophiris prostate cancer trial.

These snippets were previously published daily via twitter.

No sweat over Dermira's antiperspirant cloth

June 29

If today's US thumbs up for Dermira's anti-sweating cloth represents another example of the FDA being willing to approve most drugs as long as they are safe, the market will provide a bigger test. It cannot be denied that excessive underarm sweating – axillary hyperhidrosis, to give it its medicalised name – is an issue, but whether people will go to their doctor to get it treated on prescription, and whether insurance will pay for this, is a separate question. The Dermira product contains glycopyrronium tosylate, and is now branded Qbrexza. Evercore ISI's Umer Raffat says he was sceptical about it until the FDA hosted a workshop detailing patient stories about the social stigma of excessive sweating. The blueprint has been set by Allergan's Botox, which sells about $70m a year for hyperhidrosis and is administered via 15-20 underarm injections. Clearly Dermira's cloth offers a more convenient option, but even so the sellside consensus – 2024 sales of $239m, according to *EvaluatePharma* – seems rich. Dermira opened up 18% today, providing some comfort after its collapse in March on the failure of the acne project olumacostat glasaretil.

Novartis to spin off Alcon for half of what it paid

June 29

Novartis bought the contact lens maker Alcon from Nestlé piece by piece over the course of 2008-2011 in deals that together cost it nearly $50bn. It has now made the long-awaited decision on the unit's future, and is to spin it off in a deal likely to bring in $25bn or so. This is a continuation of the move Novartis made in 2016 to bring Alcon's eye drugs into the main company's pharmaceuticals business, which caused Alcon's sales to drop from $11bn to $6bn but allowed the unit to return to growth after several years of stagnation. Alcon will be listed on both the Swiss stock exchange and the NYSE in the first half of next year; a spin-out is regarded as the preferred option by the market, versus Novartis selling Alcon or retaining it. On a strategic level the decision makes sense, allowing Novartis to concentrate on its core of pharma, generics and biosimilars – but, even bearing in mind the near-halving of Alcon two years ago, the journey from acquisition to spin-out cannot be said to represent a success for Novartis.

Novartis's Alcon unit

	WW annual sales ($m)		
Segment	2017	2024e	CAGR
Implantables/cataract intraocular lenses	995	1,400	+5%
Consumables (other cataract surgery devices)	1,443	2,031	+5%
Equipment (other cataract surgery devices)	311	438	+5%
Vitreoretinal devices	686	951	+5%
Refractive surgery	225	439	+10%
Contact lenses	1,833	2,521	+5%
Ophthalmics OTC	-	546	N/A
Contact lens care products	531	730	+5%
Alcon total	6,024	9,056	+6%
Total company revenues	50,135	63,488	+3%

Source: EvaluateMedTech

First approval for Array with more catalysts to come

June 28

The good news for Array Biopharma was a drama-free approval from the US FDA for its Braf/Mek combo now known as Braftovi/Mektovi (encorafenib/binimetinib) in advanced melanoma. The less good news was that the label will not, for now, contain overall survival data. This might be a small concern, since many oncologists are probably already aware that the Columbus trial's overall survival readout earlier this year showed patients on the Array combination living significantly longer than those taking Roche's Zelboraf as a monotherapy. Cross-trial comparison shows that Array's combination gives numerically longer overall survival than Roche's Zelboraf/Cotellic combo or Novartis's Mekinist/Tafinlar – the figures are 33.6 months, 25.6 months at 22.3 months respectively. Even so, Array is not expected to be able to unseat the Novartis combination in the setting of Braf-positive melanoma by 2024. Neither are there any suggestions that Array will try to win on price, as Stifel analysts estimate parity or a slight premium to the Novartis combo, which costs $20,700. Array likely views colorectal cancer as a more lucrative indication – data here are due next year – and thus wants to keep its pricing options open.

Outlook for Braf/Mek combinations

Product	Company	Indication	WW 2024e sales ($m)
Tafinlar/Mekinist	Novartis	Melanoma	1,590
Braftovi/Mektovi	Array Biopharma	Melanoma	719
Braftovi/Mektovi	Array Biopharma	Colorectal cancer	906
Zelboraf/Cotellic	Roche	Melanoma	426

Source: EvaluatePharma.

Keryx gives Akebia new focus as vadadustat wait continues

June 28

The merger of equals between Akebia and Keryx will give the former a revenue stream and a sales force ready to leap into action if its big hope, vadadustat, is approved. It will also give Akebia management a talking point while the company awaits phase III data with vada, which are not due until late 2019 at the earliest. Akebia is ahead of Glaxosmithkline but behind Fibrogen in the race to get a HIF-PH inhibitor approved for anaemia in chronic kidney disease – though readout from the latter's US phase III programme with roxadustat has been delayed. Akebia will need to hit the ground running if it hopes to compete but its chief executive, John Butler, said on a conference call today that there should be room for all three products in a market he valued at $7bn. As well as Keryx's 150-strong sales force, Akebia will have help from Otsuka; the two companies will equally share the commercialisation of vada in the US, while the Japanese group also has rights in Europe and elsewhere. The remaining question is whether the Keryx merger could put off any potential Akebia acquirers – but Otsuka's involvement might have already scuppered such a deal.

US pivotal readouts for HIF-PH inhibitors

Trial	Population	ID	Data due
Roxadustat (Fibrogen) trials			
Himalayas	Dialysis dependent	NCT02052310	Year end 2018
Sierras	Dialysis dependent	NCT02273726	Year end 2018
Rockies	Dialysis dependent	NCT02174731	Year end 2018
Andes	Non-dialysis dependent	NCT01750190	Year end 2018
Olympus	Non-dialysis dependent	NCT02174627	Year end 2018
Vadadustat (Akebia) trials			
Inno2vate-Conversion	Dialysis dependent	NCT02892149	Q4 2019/Q1 2020
Inno2vate-Correction/Conversion	Dialysis dependent	NCT02865850	Q4 2019/Q1 2020
Pro2tect-Conversion	Non-dialysis dependent	NCT02680574	Mid-2020
Pro2tect-Correction	Non-dialysis dependent	NCT02648347	Mid-2020
Daprodustat (Glaxosmithkline) trials			
Ascend-D	Dialysis dependent	NCT02879305	2020
Ascend-ID	Patients initiating dialysis	NCT03029208	2020
Ascend-ND	Non-dialysis dependent	NCT02876835	2020
Ascend-NHQ	Non-dialysis dependent	NCT03409107	2020

Source: EvaluatePharma; Clinicaltrials.gov.

Nippon Shinyaku takes on Sarepta but patent questions remain

June 28

Positive phase I/II data with Nippon Shinyaku's exon 53 skipping project NS-065/NCNP-01 mean that a new rival might soon challenge Sarepta in Duchenne muscular dystrophy. But the main battle could end up being fought in the patent courts rather than the clinical trial arena. On the face of it, the Japanese group's dystrophin data look better than the phase I/II results that Sarepta reported last September with golodirsen, its exon 53 skipping candidate. But differences between the trials – including dose, duration and the methods used for measuring dystrophin – make the comparison difficult. Studies of exon 53 skippers have so far been small, but this has not stopped Sarepta from pursuing accelerated approval for golodirsen, which should give the group a head start over Nippon Shinyaku. And the two projects have similarities that could help Sarepta stall the Japanese company on intellectual property grounds: both use the phosphorodiamidate morpholino oligomers that Sarepta has claimed as its flagship technology. Sarepta's previous IP wrangle, with Biomarin, was settled last July, giving Sarepta rights to a broad patent estate in exchange for up-front payments and royalties. Maybe a similar agreement will need to be reached with Nippon Shinyaku.

Cross-trial comparison of exon 53 skipping DMD projects

Project	Company	Study	N	Mean dystrophin protein levels	ID
Golodirsen	Sarepta	4053-101 study	25	1.019% of normal at 48 weeks (30mg/kg/week)	NCT02310906
NS-065/NCNP-01	Nippon Shinyaku	US/Canada phase II trial	16	5.7% (40mg/kg/week) & 5.9% (80mg/kg/week) of normal at 24 weeks	NCT02740972
NS-065/NCNP-01	Nippon Shinyaku	Japan phase I/II trial	12	1.92% (40mg/kg/week) & 5.21% (80mg/kg/week) of normal at 24 weeks	Japic CTI-163291

Source: Company press releases.

Astra-Merck's Parp Lynparza pushes ahead in ovarian cancer

June 27

Success in the front-line Solo-1 trial is an important leap forward for Astrazeneca and Merck & Co's Parp inhibitor Lynparza; should regulatory approval follow, the drug will move into a curative setting in ovarian cancer, well ahead of Parp competitors. However, data due next year from an investigator-sponsored study could be crucial for the partners to make the most of Lynparza's head start. Solo-1 only recruited patients with a BRCA mutation, but Paola-1 recruited all-comers. The latter trial started in 2015, two years after Solo-1, by which time researchers had realised that Parp inhibitors had much broader utility. That is why rivals Abbvie and Tesaro recruited all-comers for their first-line studies, which are also due to yield data next year. Patients who harbour a BRCA gene mutation do respond much more strongly to Parp inhibition, and for this reason Solo-1 was expected to succeed; the actual survival benefit has yet to be revealed. But regulators will presumably not grant a broad label on the back of this trial alone, hence the importance of Paola-1. Analysts reckon the first-line ovarian cancer setting is a blockbuster opportunity in its own right for the Parp inhibitors and, while Astra and Merck are ahead for now, their first-mover advantage could still be blunted.

First-line ovarian Parp trials to watch

Drug	company	Trial	Important dates	Patient pool (all advanced, FIGO stage III-IV)	Trial ID
Lynparza	Astra/Merck	Solo-1	Top-line success announced June 2018	BRCA mutation post 1st line chemo.	NCT01844986
Lynparza	Astra/Merck	Paola-1	Results expected 2019	All comers post 1st line chemo plus Avastin (investigator sponsored).	NCT02477644
Zejula	Tesaro	Prima	Enrollment complete, top-line due end 2019	All comers with extreme platinum sensitivity; post 1st line chemo.	NCT02655016
Veliparib	Abbvie	Viela	Enrollment complete, top-line due early 2019*	All comers; first-line chemo +/- velaparib followed by placebo or velaparib as maintenance.	NCT02470585
Rubraca	Clovis	Athena	Due to start shortly, in collab with BMS	All comers post 1st line chemo; +/- Opdivo.	NCT03522246

*Note: FIGO=Federation of Gynecology and Obstetrics. *Primary completion data according to clinicaltrials.gov. Source: clinicaltrials.gov, company websites*

A hit and a miss for Achaogen

26 June

Any hope that the US FDA would overrule its expert advisers and approve plazomicin in two infectious disease indications has been dashed. The agency has approved plazomicin, which now has the brand name Zemdri, in complicated urinary tract infections (cUTIs). However, it also sent sponsor Achaogen a complete response letter for a second indication, bloodstream infections caused by carbapenem-resistant enterobacteriaceae because the trial supporting it did not show sufficient evidence of efficacy. This mirrors the votes of an FDA advisory committee, which unanimously supported approval in cUTI but voted 11-4 against its use in bloodstream infections. Achaogen's 20% share price drop in early trading today suggests that some investors were betting on approvals in both.

Good things come in small packages for Glaukos

26 June

The FDA has approved the smallest-ever medical device: the injectable form of Glaukos's iStent. The approval has driven the company's shares up 4% so far today – unsurprising, since Stifel analysts suggest that the injectable form could come with a 10% price bump over the initial iteration of the iStent, approved in the US in 2012. Over time, around 80% of iStent sales could move from the first iStent to the injectable form, given the better delivery profile – the original version is placed using a special inserter in a more cumbersome procedure. The device, like its predecessor, is a tiny tube placed in the eye via a needle to drain fluid and thereby reduce intraocular pressure. It is intended for use in adults with mild-to-moderate primary open-angle glaucoma who are undergoing concomitant cataract surgery. The new device will launch in the third quarter, and, crucially, looks likely to beat Ivantis's rival Hydrus device to market.

Glaukos's WW Annual Sales ($m)

2017	2018e	2019e	2020e	2021e	2022e	2023e	2024e	CAGR
160	184	225	265	305	345	385	426	+15%

Source: EvaluateMedTech

The iStent inject. Picture courtesy of Glaukos.

Death stalls Sophiris prostate cancer trial

25 June

It is difficult to slip news of a death into an otherwise promising clinical trial update and not see a negative response, as Sophiris Bio learned this morning. Shares in the California-based company sunk 42% this morning after it disclosed that a single patient in a phase II prostate cancer trial had died on the same day as receiving his second dose of topsalysin (PRX302). Trial investigators have now suspended all second doses of the PSA regulator, which had so far been dosed in 450 patients. In 35 patients who had undergone a biopsy after treatment with a single dose of topsalysin, 10 showed a clinical response as defined by no detectable tumour or reduction to clinical insignificance. Those data will be irrelevant, of course, if the patient death is found to be medication-related and Sophiris is forced to discontinue work. Topsalysin is being tested in patients with localised prostate cancer, for which other treatment options are surgery, radiotherapy or brachytherapy. Sophiris has no other listed pipeline projects. According to *EvaluatePharma* only two other PSA regulators are known to be in development – G-114 and G-115, preclinical assets of Inspyr Therapeutics.

PSA regulators in development

Status	Product	Company	WW sales ($m) 2024e
Phase II	Topsalysin	Sophiris Bio	30
Pre-clinical	G-115	Inspyr Therapeutics	-
	G-114	Inspyr Therapeutics	-

Source: EvaluatePharma

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