Evaluate Vantage

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Snippet roundup: A poor week for Sanofi and a worse one for Teva

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

This week, October 30 to November 3, 2017, we had thoughts on the following: Sanofi signals further Lantus woes with biosimilar substitutability prediction; Just when you thought it couldn't get worse at Teva; Orbusneich's Harmonee data are strangely discordant; Astra deal could give new Incyte into IDO; Second Keytruda delay – embarrassment rather than catastrophe?

These snippets were previously published daily via twitter.

Sanofi signals further Lantus woes with biosimilar substitutability prediction

November 2, 2017

Sanofi's third-quarter results amply illustrated just how difficult the diabetes market has become for the big insulin players. Lantus sales slumped 16% on the same period last year, and the French drug maker warned that the fourth quarter is unlikely to look much prettier. None of this was entirely unexpected, although analysts sat up sharply on the company's conference call when executives mentioned that they believe biosimilar insulins could become substitutable by 2020. This would put a significantly bigger squeeze on the franchise than is currently expected – analysts at Bernstein commented that neither they nor consensus model this as occurring in this timeframe. *EvaluatePharma*'s consensus of sellside numbers already has US sales of Lantus sliding 26% from 2020 to 2022, presumably a picture that could worsen if substitutability is sanctioned. The product is still expected to be its second-biggest seller in 2022 so this is no small matter. And while Sanofi's prediction is likely to be a worst-case scenario, the regulatory and political climate in the US is increasingly primed to aid the approval and uptake of lower cost alternatives to expensive branded drugs. The pressure on Sanofi to bolster its top-line growth just ratcheted up another notch.

Long-acting insulins - will substitutability change the picture from 2020?

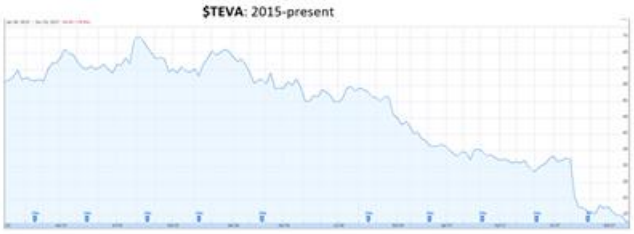
		Annual US sales ($m)		
Product	Company	2020	2021	2022
Tresiba	Novo Nordisk	1,393	1,591	1,771
Lantus	Sanofi	1,438	1,253	1,070
Toujeo	Sanofi	884	952	1,016
Levemir	Novo Nordisk	852	744	652
Basaglar (Lantus biosimilar)	Eli Lilly	622	627	635
Lusduna Nexvue (Lantus biosimilar)	Merck & Co	121	180	231

Source: EvaluatePharma

Just when you thought it couldn't get worse at Teva

November 1, 2017

It is kitchen sink time at Teva, and only drastic action from new chief executive Kåre Schultz is likely to restore investor confidence. After years of leaning on Copaxone and generics to carry the company, Teva needs to alter its strategy. Mr Schultz will probably look at a range of options including simply beefing up to generate growth or slimming down to prop up earnings. More dramatic shifts like a breakup to divide the group's innovative or developmental assets like Austedo and fremanezumab from mature products like Copaxone and its generics business should enter the frame. On Mr Schultz's second day in the job, the Israel-based group unleashed a barrage of bad news with its third-quarter earnings report in the form of lowered guidance both on its branded flagship Copaxone and its generics lines, along with ominous words about its schedule for paying down the debt it accrued from buying Allergan's generics business. Teva's shares have already been battered this year, but they plunged another 19% in early US trading today – falling to a price they had not seen since 2000 – after the group cut its annual profit guidance a second time this year and revealed a substantial deterioration in gross profit margins. The $60bn loss in valuation since its peak in mid-2015 exceeds the $40.5bn price Teva paid for the Allergan generics business at about the same time.



Orbusneich's Harmonee data are strangely discordant

November 1, 2017

Orbusneich's unusual Combo stent, which is coated with an antiproliferative drug but also with anti-CD34 antibodies designed to capture circulating endothelial progenitor cells to aid healing, is approved in Europe but not the US. Orbusneich is hoping to change that – but results of the Harmonee trial released at the TCT meeting yesterday, might not be much help. Though Harmonee was technically a success, showing Combo to be non-inferior to the gold standard DES, Abbott's Xience, Combo was numerically poorer on the primary endpoint of target vessel failure rate at one year, at 7% versus 4.2% with Xience. In-stent late loss after one year was 0.29mm with Combo and 0.22mm with Xience, and the rate of in-stent restenosis – a reduction of more than 50% in the post-stenting vessel diameter – was lower with Combo, at 1.3% compared with 2.6% for Xience. Orbusneich plans to use the Harmonee data to support an approval filing in Japan, and to move forward in the US.

OrbusNeich's COMBO stent

Astra deal could give new Incyte into IDO

October 31, 2017

On the face of it, yesterday's deal between Astrazeneca and Incyte is just another example of a big pharma group trying to get in on the IDO/PD-(L)1 combo action. But a closer look at ongoing trials in this space suggests that there could soon be an answer to the question of just how much benefit comes from adding IDO inhibition – the Astra/Incyte agreement outlines a phase III study with a control arm in which patients will receive Astra's PD-L1 inhibitor Imfinzi alone. The trial, in stage III non-small cell lung cancer, is due to start in the first half of 2018, so results will not be available for a while. In the meantime, the Echo-301 study of Incyte's epacadostat and Merck & Co's Keytruda is set to read out early next year – that also includes a Keytruda-only control arm, but is trialling the combo in melanoma. And a handful of other controlled studies are under way, most of which also involve Keytruda. But these are still outnumbered by single-arm trials of PD-(L)1/IDO combos, which could yield data of relatively limited interest.

IDO + PD-(L)1 combo trials

PD-(L)1 inhibitor	Company	Trial	Comparator arm	ID
Epacadostat (Incyte)				
Imfinzi	Astrazeneca	Phase III in stage III NSCLC	Imfinzi	Uknown
Imfinzi	Astrazeneca	Echo-203, phase I/II in solid tumours	No comparator	NCT02318277
Keytruda	Merck & Co	Keynote-252/Echo-301, phase III in melanoma	Keytruda	NCT02752074
Keytruda	Merck & Co	Phase III in NSCLC	Keytruda	NCT03322540
Keytruda	Merck & Co	Phase III in NSCLC	Keytruda + chemo	NCT03322566
Keytruda	Merck & Co	Keynote-679/Echo-302, phase III in mRCC	Sutent or Votrient	NCT03260894
Keytruda	Merck & Co	Phase II in thymic carcinoma	No comparator	NCT02364076
Keytruda	Merck & Co	Phase I/II in colorectal cancer	No comparator	NCT03182894
Keytruda	Merck & Co	Echo-206, phase I/II in solid tumours	No comparator	NCT02959437
Keytruda	Merck & Co	Keynote-037/Echo-202, phase I/II in various cancers	No comparator	NCT02178722
Keytruda/Opdivo	Merck & Co/Bristol-Myers Squibb	Echo-207, phase I/II in solid tumours	No comparator	NCT03085914
Opdivo	Bristol-Myers Squibb	Echo-204, phase I/II in advanced cancers	No comparator	NCT02327078
Tecentriq	Roche	Echo-110, phase I in urothelial carcinoma	No comparator	NCT02298153
Indoximod (Newlink Genetics)				
Keytruda/Opdivo	Merck & Co/Bristol-Myers Squibb	Phase II/III in metastatic melanoma	PD-1 inhibitor	NCT03301636
Keytruda/Opdivo	Merck & Co/Bristol-Myers Squibb	Phase I/II in metastatic melanoma	No comparator	NCT02073123
GDC-0919/Navoximod (Newlink Genetics)*				
Tecentriq	Roche	Phase I in solid tumours	No comparator	NCT02471846

*Roche handed back rights to navoximod in June 2017. Source: EvaluatePharma; clinicaltrials.gov

Second Keytruda delay – embarrassment rather than catastrophe?

October 30, 2017

Merck & Co's decision after market close on Friday to pull its EU filing for Keytruda in first-line lung cancer is mysterious. Did the company realise that the drug was not approvable in this setting without data from the controlled Keynote-189 trial and, having on Friday delayed the '189 readout by over a year, feel compelled to formalise the EU delay? Or was it that the original filing was a no-hoper and, conversely, feedback from the European regulator prompted it to delay Keynote-189? Either way, the move looks embarrassing, and

apparently Merck had intended to leave it to the CHMP to announce that the filing had been withdrawn, but since the subject was mentioned on its third-quarter call it decided to issue its own statement. Keynote-189 readout has been delayed because of overall survival being promoted to a co-primary endpoint – something Merck might have realised was vital for EU approval. Still, analysts thought the Keynote-021G trial – whose remission rate benefit served for accelerated US approval – was always going to be a long shot in the EU, and it is only EU sales that are at stake at present; US first-line NSCLC approval looks highly unlikely to be rescinded.

Keytruda in 1st-line NSCLC - another US vs EU conflict

Study	Detail	US relevance	EU relevance	Trial ID
Keynote-021G	ORR for Keytruda + pemetrexed/carboplatin of 55%, vs 29% for pemetrexed/carboplatin alone	Basis for accelerated approval on 10 May 2017	Deemed insufficient for approval; filing withdrawn 27 Oct 2017	NCT02039674
Keynote-189	Keytruda on top of cisplatin/carboplatin; OS added to PFS as co-primary endpoint, delaying readout from Q4 2017 to Feb 2019	Likely needed to convert accelerated approval into full approval	Likely needed for approval	NCT02578680

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