Evaluate Vantage

February 16, 2018

Snippet roundup: Alzheimer's doubts grow and Bavencio's Javelin falls short

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

This week, February 12-16, 2018, we had thoughts on the following: Exparel knockback means more pain for Pacira; orphan drug status hints at a new use for Mek inhibitor; Bavencio must jump bigger hurdles than the failure of Javelin Lung 200; Biogen's trial tinkering adds to Alzheimer's jitters; Shire puts number on Hemlibra threat; new Merck Alzheimer's stumble sets low BACE; DBV up on claims of FDA reprieve; Galmed's Nash prospects vanish with academic-sponsored study flop.

These snippets were previously published daily via twitter.

Exparel knockback means more pain for Pacira

February 16, 2018

Appealing to the US FDA's benevolent stance to drug approvals is now Pacira's only hope to get its lead drug, Exparel, additionally approved as a nerve block agent this year. The still bullish company's insistence that it was "working with the FDA towards the April 6, 2018, PDUFA date" notwithstanding, Exparel has yesterday's 6-4 adcom vote against approval to add to a 2014 complete response letter, and approval would require the agency to go against the negative advice of the panel. Analysts seem unconvinced, and the stock was off 14% in today's premarket. Leerink pointed to panellists' doubts about the shortcomings of "conflicting and confounding" phase III data; after the complete response letter Pacira had conducted two pivotal trials, but only one succeeded. Leerink previously expected $200m of Exparel's $600m peak sales to come from the nerve block indication – the drug is separately approved in postsurgical anaesthesia – but later scaled this back to $100m. Among the likely outcomes are the running of additional trials, and generating more comprehensive safety data and support for an opioid-sparing effect, so perhaps all near-term expectations of nerve block sales now need to be eliminated.

Orphan drug status hints at a new use for Mek inhibitor

February 15, 2018

The Mek inhibitors Mekinist and Cotellic are marketed in combination with Braf-targeting drugs for Braf/Mek-positive melanoma, but the rare neurological disease neurofibromatosis type 1 today emerged as a possible new use. This was after Astrazeneca/Merck & Co/Array's Mek inhibitor selumetinib secured US orphan drug status for this genetic disorder, which is characterised by the growth of benign tumours along nerve cells. Close examination of the Clinicaltrials.gov database reveals significant work in neurofibromatosis type 1, including studies involving several Mek inhibitors. However, these all have academic primary sponsors, with biopharma groups featuring as collaborators in some. Selumetinib's orphan drug status presumably signals willingness on the part of pharma to get in on the act.

Selected trials of Mek inhibitors in neurofibromatosis type 1

Compound	Industry owner	Primary sponsor	Enrolment target	Trial ID
Selumetinib	Astrazeneca/Merck & Co/Array	NCI	20	NCT03109301
Selumetinib	Astrazeneca/Merck & Co/Array	Great Ormond Street Hospital	30	NCT03326388
Selumetinib	Astrazeneca/Merck & Co/Array	NCI	104	NCT01362803
Selumetinib	Astrazeneca/Merck & Co/Array	Sarcoma Alliance for Research through Collaboration	21	NCT03433183
Selumetinib	Astrazeneca/Merck & Co/Array	NCI	24	NCT02839720
Mekinist	Novartis	University of California, San Francisco	27	NCT03232892
Mekinist	Novartis	St. Justine's Hospital	150	NCT03363217
Binimetinib	Array	University of Alabama at Birmingham	20	NCT03231306

Source: Clinicaltrials.gov

Bavencio must jump bigger hurdles than the failure of Javelin Lung 200

February 15, 2018

Keen followers of immuno-oncology trials no doubt recognise the first-line lung cancer dominance of Merck & Co's Keytruda, with Roche's Tecentriq and Astrazeneca's Imfinzi mounting a strong challenge. As such they will be quick to dismiss Pfizer/Merck KGaA's Bavencio, especially given today's failure of this drug in the Javelin

Lung 200 trial. However, this was a study in second-line patients, a setting in which it is now virtually impossible to run an I-O study, given the increasing availability of Keytruda first line, and the second-line market being carved up by Keytruda, Tecentriq and Bristol-Myers Squibb's Opdivo. Indeed, Merck KGaA today pointed to a large number of control-arm subjects in Javelin Lung 200 crossing over to other anti-PD-(L)1 drugs as a confounding factor. For Bavencio the far more important readout is that of Javelin Lung 100, in the first-line setting – for the outcome of which the 200 trial has no read-across. However, after design changes in light of the furious pace of progress in this setting readout of 100 was delayed to mid-2019. The risk is that by the time 100 yields data it will, like 200, be irrelevant.

Selected lung cancer trials of Pfizer/Merck KGaA's Bavencio

Study	Setting	Design	Data	Trial ID
Javelin Lung 200	2nd-line, PD-L1+ve NSCLC	Bavencio vs docetaxel in 750 subjects	Failed to extend OS	NCT02395172
Javelin Lung 100	1st-line, PD-L1+ve NSCLC	Bavencio vs platimum chemo in 1,095 subjects	OS & PFS co-primaries, primary completion Jul 2019	NCT02576574

Biogen's trial tinkering adds to Alzheimer's jitters

February 15, 2018

When it comes to Alzheimer's, any hint of a problem can make investors jittery. So that explains why news that Biogen had added 510 patients to its two pivotal trials of aducanumab sent the company's stock down 7% yesterday. Biogen said the move was necessary to maintain statistical power after seeing more variability than expected on the primary endpoint; one conclusion is that the difference between the treatment and control arms is so small that more patients are needed to tease out a statistical benefit. While tinkering with trials is usually a bad sign, Mizuho's Salim Syed tried to convince investors that it might not mean the worst. He pointed out that, when the studies were designed in 2015, aducanumab was in a race with Lilly's solanezumab, so Biogen chose to make its trials as efficient as possible, but with an option to increase their size after a pre-planned analysis. He also highlighted faster than expected enrolment – Biogen still expects to complete this by mid-2018 – and a low drop-out rate. It will be a while before the truth will become clear – the trials remain blinded, with data now expected by early 2020.

Aducanumab's phase III trials

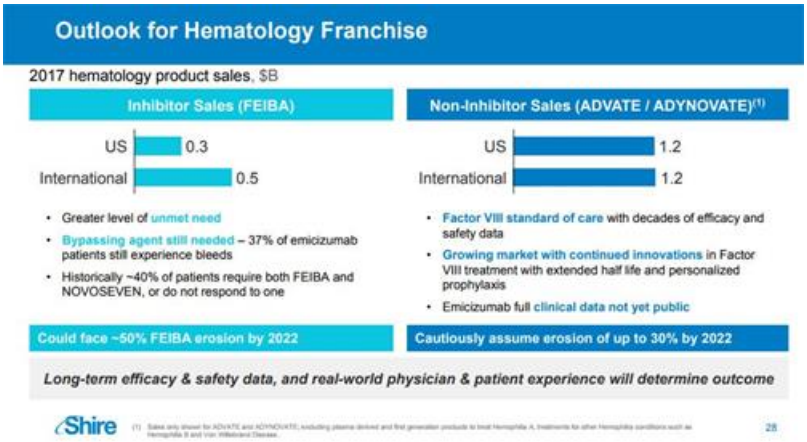
Trial	New n	Primary endpoint	ID	Previous primary completion
Engage	1,605	Clinical Dementia Rating Scale – Sum of Boxes	NCT02477800	Nov 2019
Emerge	1,605	Clinical Dementia Rating Scale – Sum of Boxes	NCT02484547	Feb 2020

Source: Clinicaltrials.gov

Shire puts number on Hemlibra threat

February 14, 2018

It has long been known that Shire's haemophilia business will suffer with the entry of Roche's bispecific antibody Hemlibra – the question has been how much. Today Shire tried to put a number on the threat it faces, saying it expects sales of its factor VIII therapies to drop by up to 30% between now and 2022. These products are used in haemophilia A patients who have not developed inhibitors, a population for which Hemlibra is not yet approved but could be soon; Roche announced a win in the Haven 3 trial in these patients in November. Shire executives stressed that they had not seen full Haven 3 data and were not sure when these might be reported – analysts have speculated that the data might be presented at the World Federation of Hemophilia meeting in Glasgow in May, but Roche has not confirmed this. Meanwhile, in patients who have developed inhibitors, where Hemlibra already has US approval, Shire is expecting 50% erosion in its Feiba business by 2022. Shire shares were down 2% today on weak 2018 guidance as the company invests in a new US plasma manufacturing site.



New Merck Alzheimer's stumble sets low BACE

February 14, 2018

It seems that nothing will kill off the amyloid hypothesis of Alzheimer's – not even the latest failure of Merck's

BACE inhibitor verubecestat, this time in prodromal disease. The halt of the Apecs trial dents the theory that treating patients early, before full-blown Alzheimer's develops, could be the way forward. But some companies are going even earlier, into asymptomatic, at-risk patients. The latest blow to verubecestat, a year after it tanked in mild to moderate disease, cannot bode well for the next late-stage BACE candidate, Lilly and Astrazeneca's lanabecestat, which is being studied in mild and early Alzheimer's. If the "earlier is better" brigade is right, BACE hopes might rest with Johnson & Johnson's JNJ-54861911 and Novartis/Amgen's CNP520, both of which are being tested in asymptomatic people with a family history of Alzheimer's or who carry the APOE4 gene. However, trials are not due to read out until 2023. Up sooner is VTV's Rage inhibitor azeliragon, which targets amyloid, Tau and inflammation, with phase III results due in April. But the data everyone is waiting for are with Biogen's anti-amyloid MAb aducanumab, which will come next year [this has since been delayed until 2020].

Selected BACE inhibitors in clinical development

Project	Company	Phase	Trial(s)	ID	Primary completion
Lanabecestat	AstraZeneca/Lilly	III	Daybreak-Alz; mild AD Amaranth; early AD	NCT02783573 NCT02245737	Both Sep 2019
Elenbecestat (E2609)	Eisai/Biogen	III	MissionAD1; early AD MissionAD2; early AD	NCT02956486 NCT03036280	Both Nov 2020
JNJ-54861911	Johnson & Johnson/Shionogi	II/III	Dian-Tu; at risk Early; at risk	NCT01760005 NCT02569398	Dec 2023 Apr 2024
CNP520 + CAD106	Novartis/ Amgen	II/III	Generation S1; at risk	NCT02565511	May 2024
CNP520	Novartis/ Amgen	II/III	Generation S2; at risk	NCT03131453	Jul 2024
LY3202626	Lilly	II	Navigate-AD; mild AD	NCT02791191	Jun 2019

DBV up on claims of FDA reprieve

February 14, 2018

DBV Technologies' hope that the failed Pepites trial of its peanut allergy patch could still support US approval appear to be well founded – according to the company the FDA will accept its existing data package for Viaskin Peanut, sending DBV's stock up 40% this morning. However, the French group has not made the FDA's communication public. DBV plans to file the patch in the second half of the year, but even if approved it could face stiff competition from Aimmune's rival oral project, AR101, which is due to report data from the phase III Palisade trial this month. If the agency's stance is indeed as lenient as DBV suggests, this could mean that even if AR101 disappoints the FDA might still agree to review it. The Pepites trial reported a response rate of 35% with Viaskin Peanut – this was significantly significant versus placebo, but was not enough to meet the confidence interval threshold agreed with the FDA. There is room for both therapies in the market, Leerink analysts believe, citing DBV's ease of use and safety profile. How the projects stack up in terms of efficacy could soon become clearer.

Galmed's Nash prospects vanish with academic-sponsored study flop

February 14, 2018

Galmed's protestations notwithstanding, the markets today wrote off the value of the group's lead asset, Aramchol, in the liver disease Nash. This followed the failure of Arrive, an investigator-sponsored trial of Aramchol in non-alcoholic fatty liver disease (NAFLD) in HIV patients. The trial was relevant because it measured liver fat reduction by MRI and did not include liver biopsies; Galmed had earlier eschewed liver biopsies in Nash trials, saying these were risky and costly, and had intended to position Aramchol in early Nash. Still, Aramchol's hotly awaited Arrest trial in Nash does use liver biopsy to confirm Nash at enrolment. The group had earlier dismissed NAFLD as not being a real disease, and today it argued that HIV-related NAFLD pathogenesis might differ from that of "garden-variety Nash". It might be that 12 weeks was too short a time to detect a benefit in Arrive. Arrest, which measures liver triglyceride concentration by nuclear magnetic resonance spectroscopy (NMRS) over 52 weeks, is due to read out in the second quarter. Unimpressed investors sent Galmed stock down 50% this morning.

Selected trials of Aramchol

Study	Trial ID	Enrolment	Result
Arrive	NCT02684591	50 HIV subjects with NAFLD	Failed to improve hepatic steatosis assessed by MRI at 12 weeks
Arrest	NCT02279524	248 Nash subjects	Nash confirmed by liver biopsy. Primary endpoint measured by NMRS at 52 weeks. Data Q2 2018

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