Evaluate Vantage

September 15, 2017

Snippet roundup: Bad news for Sage and Santhera, good tidings for Glaxo and Bayer

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

This week, September 11 to 15, 2017, we had thoughts on the following: European rejection sidelines Santhera; Bayer writes PI3K second act with Aliqopa; unanimous Shingrix backing points towards Glaxo vs Merck vaccine battle; Sage takes hit on epilepsy and bets the house on depression; ICER counters Amgen's rosy Repatha cost-effectiveness view; Allergan's patent end-run likely to draw lawmakers' attention; lampa no complement to eye-disease space.

These snippets were previously published daily via twitter.

European rejection sidelines Santhera

September 15, 2017

A European knockback for Santhera's Raxone in Duchenne muscular dystrophy leaves the company's future looking precarious. The Swiss group had just SFr78m ($81m) in cash at the end of June and is committed to a US trial that is not due to read out until 2019. Santhera's share price plunged 40% this morning on news of the negative opinion from the EMA's Committee for Medicinal Products for Human Use, which concluded that the phase III Delos trial in patients not using corticosteroids did not provide enough evidence of efficacy. This echoes the stance from the FDA, which asked for a new study in patients taking corticosteroids before it would consider Santhera's application. That trial, Sideros, is recruiting, and it is unclear whether it could also support eventual European approval. Santhera, meanwhile, says it plans to appeal against the CHMP's decision. The group still has European sales of Raxone in Leber's hereditary optic neuropathy, which totalled SFr10.9m in the first half of 2017, but DMD is the real prize – the project had been forecast to become the second-biggest DMD drug by 2022. There had been concerns that, if approved, Raxone could be scuppered by the existence of supplements with the same active ingredient, idebenone – but the latest rejection makes Santhera's problems more immediate.

Top DMD products in 2022

		WW indication sales ($m)				
Product	Company	2016	2018	2020	2022	WW indication status
Exondys 51	Sarepta Therapeutics	5	208	461	583	Marketed
Raxone	Santhera Pharmaceuticals	-	44	183	401	Rejected (EU), phase III (US)
Translarna	PTC Therapeutics	81	145	183	117	Marketed (EU)
WVE-210201	WAVE Life Sciences	-	-	-	116	Pre-clinical
SRP-4045	Sarepta Therapeutics	-	-	14	66	Phase III
SRP-4053	Sarepta Therapeutics	-	-	14	66	Phase III

Source: EvaluatePharma

Bayer writes PI3K second act with Aliqopa

September 15, 2017

The resurgence of PI3K inhibitors continues with the approval of Bayer's copanlisib, which will be marketed as Aliqopa, in relapsed follicular lymphoma. The drug is forecast to become the biggest in its class, but the product to beat in the leukaemia/lymphoma space is Abbvie/Johnson & Johnson's Imbruvica, which is forecast to bring in $7.6bn in 2022 compared with Aliqopa's $373m. Still, Aliqopa can make the most of a favourable safety profile versus Gilead's Zydelig, previously the only PI3K inhibitor to reach the market. The latter carries warnings about liver, gastrointestinal and other toxicities that have contributed to its disappointing commercial performance and led to pessimism about this drug class. But PI3Ks are back on the up after Verastem's recent success with duvelisib in leukaemia and lymphoma and Roche's positive Esmo presentation with taselisib in breast cancer. Sales from drugs in this class now are expected to exceed $1bn in 2022, although Aliqopa's launch trajectory will be closely watched to determine whether this outlook is justified.

PI3K inhibitor outlook

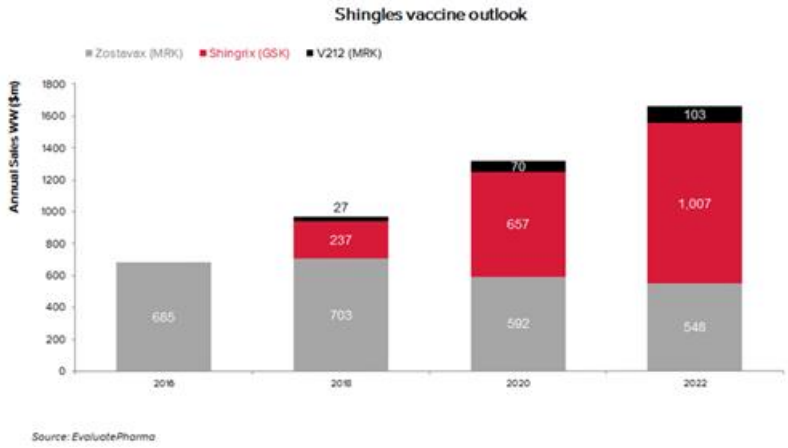
Company	Product	Generic Name	Pharmacological Class	Annual Sales WW ($m) 2016	2018	2020	2022	WW Phase (Current)
Bayer	Aliqopa	copanlisib	PI3K inhibitor	-	34	173	373	Approved
MEI Pharma	ME-401	-	PI3K delta inhibitor	-	-	43	205	Phase I
TG Therapeutics	TGR-1202	umbralisib tosylate	PI3K delta inhibitor	-	-	15	175	Phase III
Gilead Sciences	Zydelig	idelalisib	PI3K delta inhibitor	168	152	162	162	Marketed
Novartis	BYL719	alpelisib	PI3K alpha inhibitor	-	-	49	153	Phase III
Roche	Taselisib	taselisib	PI3K inhibitor	-	-	10	75	Phase III
Verastem	Duvelisib	duvelisib	PI3K gamma & delta inhibitor	-	3	28	64	Phase III
Novogen	GDC-0084	-	PI3K inhibitor	-	-	-	21	Phase I
UCB	Seletalisib	seletalisib	PI3K delta inhibitor	-	-	-	2	Phase II

Source: EvaluatePharma

Unanimous Shingrix backing points towards Glaxo vs Merck vaccine battle

September 14, 2017

Glaxosmithkine's Shingrix is reckoned to become the biggest-selling shingles vaccine by 2022, and indeed with a forecast just cracking $1bn could become a bigger product than its chief competitor, Merck & Co's Zostavax. Unanimous backing by a US FDA advisory committee puts this scenario one step closer, although there remain questions over how well it will perform commercially. For one, the two-dose regimen and systemic side effects raise questions over its real-world performance, compared with a clinical trial setting where compliance tends to be better. Another commercial concern is how Merck responds on price – Zostavax now sits on tier 3 of many Medicare prescription drug plans, requiring a higher copay, but the company could conceivably manoeuvre its way onto lower tiers by cutting its price. On the other hand, as a live attenuated vaccine, Zostavax is not recommended for use in immunocompromised people, which Glaxo hopes will not be an issue with its non-live recombinant vaccine. The FDA is expected to decide on approval in October.



Source: EvaluatePharma

Sage takes hit on epilepsy and bets the house on depression

September 12, 2017

Those Sage Therapeutics investors who did not sell today on news of brexanolone's phase III failure in super-refractory status epilepticus (SRSE) are relying on hope that trials in notoriously difficult mood disorder indications will be more fruitful. Brexanolone, also known as Sage-547, is due to have readouts by the end of the year in post-partum depression and major depressive disorder – Sage is pretty much betting its immediate future on these two studies as it has decided to discontinue most work in SRSE. Most optimism lies in post-partum depression, which generated encouraging phase II data albeit in 21 patients. The phase III programme has enroled 220 patients, and Leerink analysts believe that a minimum threshold for clinical success would be a 4-6 point difference from placebo on the Hamilton Depression Rating Scale 17, although that small statistical difference may not make it a commercial success. In phase II, the difference was 11 points. This success will be essential to support Sage's lofty $2.8bn market capitalisation, which was down 15% following the news that brexanolone had failed in SRSE, its first phase III test.

SAGE-547 (brexanolone) trials

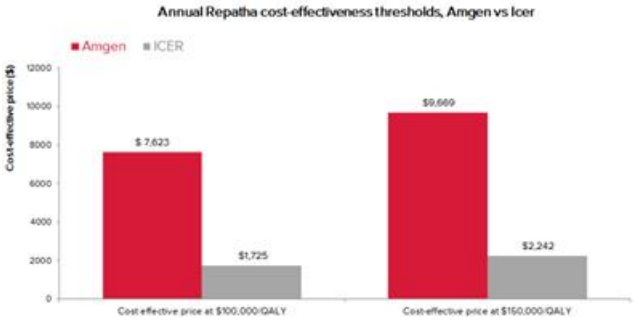
Study	Trial ID
Super-Refractory Status Epilepticus	NCT02477618
Hummingbird trials: severe postpartum depression	NCT02942004
Moderate postpartum depression	NCT02942017

ICER counters Amgen's rosy Repatha cost-effectiveness view

September 11, 2017

Amgen needs to cut the net price of Repatha by at least 85% to meet commonly used cost-effectiveness guidelines, the leading US public reviewer of drug prices says. The Institute for Clinical and Economic Review's new analysis, based on the Fourier cardiovascular outcomes trial, says based on clinical evidence Repatha needs to have a price of $2,242 to yield a cost of $150,000 per quality adjusted life year in heart disease

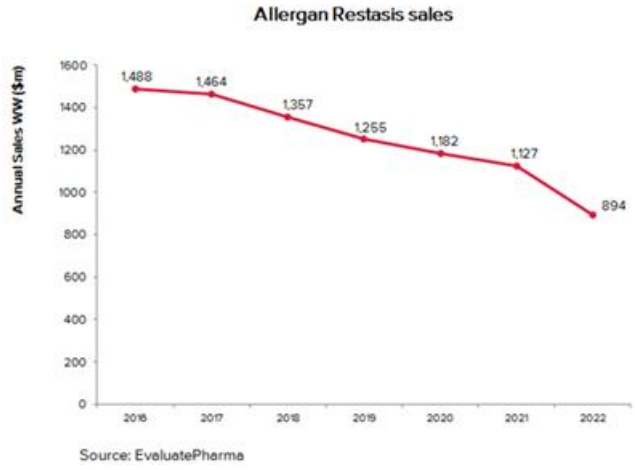
patients with elevated LDL and current use of statins. ICER's previous review of Repatha set a higher threshold of $5,300-7,600 – however, that was based on a meta-analysis of the less robust phase III trials Amgen had used to achieve US FDA approval. The Fourier trial yielded a 15% reduction in risk of cardiovascular events, although that result was driven by myocardial infarctions and stroke, not mortality; the older pill Zetia combined with statins yields a similar result. Last month, Amgen published its own cost-effectiveness assessment in JAMA Cardiology, which found that a price of $9,669 – similar to Repatha's average net price in the US – would meet a cost-effectiveness threshold of $150,000.



Allergan's patent end-run likely to draw lawmakers' attention

September 11, 2017

Allergan's decision to domicile the intellectual property of Restasis with a Native American tribe is a novel strategy that does not seem likely to survive as a loophole to delay patent expiry. The announcement on Friday said the St Regis Mohawk Tribe, a sovereign entity, would receive $13.75m up front and $15m in annual revenues on sales of the dry eye drops, and in return would file a motion to dismiss Mylan's inter partes action based on sovereign immunity claims. In cases involving the Universities of Florida and Maryland, the Patent Trial and Appeals Board ruled that state sovereignty applies to inter partes reviews of intellectual property. Should the inter partes review fail, generic competition could be delayed until 2024. Bernstein analyst Ronny Gal said it was unclear whether this strategy would withstand legal challenge, since unlike the universities the Mohawk tribe did not own the rights when the IPR was challenged. In any case, Allergan had been approached by a law firm to test this strategy, and other pharma groups are likely to follow suit. This strategy will likely draw the attention of national lawmakers, who have leaned towards encouraging greater generic competition as a way to restrain drug price increases. It would not be surprising to see legislation to limit the use of this mechanism, particularly if Allergan prevails.



Lampa no complement to eye-disease space

September 11, 2017

The eye project lampalizumab looks like it might not live up to the sellside's expectations as Roche's second-biggest pipeline asset. In the phase III Spectri trial, lampalizumab missed its primary endpoint of reducing the mean geographic atrophy lesion area in patients with dry age-related macular degeneration (AMD) when compared with a sham treatment. The complement-D antibody is in a second trial called Chroma that is due to read out in November. A best-case scenario is that Roche would successfully have to complete a third phase III trial of lampalizumab for it to achieve regulatory approval – delaying launch until 2020 or 2021 – although conceivably the long-term safety extension that combines patients from both Spectri and Chroma could generate persuasive data. No specific treatments for dry AMD exist, although other complement factor inhibitors are in the pipeline, including Ophthotech's Zimura and Novartis's tesidolumab. Ophthotech's already battered shares fell 15% Friday on Roche's announcement, which investors took as bad tidings for Zimura.

Selected dry age-related macular degeneration candidates

Product	Company	Pharmacological Class
Phase III		
Lampalizumab	Roche	Anti-complement factor D MAb
Zimura	Ophthotech	Anti-complement factor C5a aptamer
Phase II		
Alphagan P (intravitreal implant)	Allergan	Alpha 2 adrenoceptor agonist
Tesidolumab	Novartis	Anti-complement factor C5 MAb
CNTO 2476	Johnson & Johnson	Anti-immunoglobulin G (IgG) MAb
MA09-hRPE Cellular Therapy	Astellas Pharma	Stem cell therapy
OpRegen	BioTime	Retinal pigmented epithelial (RPE) cell therapy
MA09-hRPE Cellular Therapy	CHA Bio & Diostech	Stem cell therapy
CLG561	Novartis	Eye preparation
APL-2 Intravitreal	Apellis Pharmaceuticals	Complement factor C3 inhibitor

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