Evaluate Vantage

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Abbvie’s Jak flashes a warning for the whole class

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Just when Lilly determined to press ahead with its Jak inhibitor Olumiant, more fears have emerged that most of the class could be doomed in its biggest use, rheumatoid arthritis.

The concerns came yesterday from updated findings with Abbvie’s Jak competitor upadacitinib, suggesting that the risk of thrombotic events is even greater than feared. The fallout could also hit Gilead’s filgotinib and, with the sellside expecting upadacitinib and Olumiant to play important roles in RA, differently acting injectables could be the obvious beneficiaries (see tables below).

Indeed, sellside consensus data from *EvaluatePharma* suggest that, of the assets currently in development, upadacitinib will in 2022 represent the biggest-selling RA drug. With expected 2022 revenue of $574m in RA Olumiant appears eleventh overall.

Top 10 rheumatoid arthritis products in 2022

				Global sales ($bn)	
Product	**Company**	**Pharma class**	**Status**	**2016**	**2022e**
Humira	Abbvie/Eisai	Anti-TNFa MAb	Marketed	5.6	4.5
Enbrel	Amgen/Pfizer/Takeda	TNFa inhibitor	Marketed	6.4	3.9
Simponi	Johnson & Johnson/ Merck & Co	Anti-TNFa MAb	Marketed	1.9	2.5
Actemra	Roche	Anti-IL-6 MAb	Marketed	1.4	1.9
Orencia SC	Bristol-Myers Squibb/ Ono	T-cell costimulation blocker	Marketed	1.2	1.6
Xeljanz	Pfizer	Jak 3 inhibitor	Marketed	0.9	1.3
Upadacitinib	Abbvie	Jak 1 inhibitor	Phase III	-	1.2
Cimzia	UCB	Anti-TNFa MAb	Marketed	1.0	1.0
Orencia	Bristol-Myers Squibb	T-cell costimulation blocker	Marketed	1.2	0.9
Kevzara	Sanofi	Anti-IL-6R MAb	Marketed	-	0.6

Source: EvaluatePharma.

The Lilly drug is approved in the EU, but has been knocked back with a US complete response letter. On yesterday’s third-quarter earnings call Lilly said it was accumulating data for resubmitting the asset; as for thromboembolic events specifically, it said real-world evidence pointed to this adverse event being consistent with “background rates in the RA patient population”.

Late-breaking shocker

All does not seem to be business as usual, however, judging by late-breaking abstracts for next month’s American College of Rheumatology meeting, which went live this week.

Among these appeared 12-week extension data in upadacitinib’s Select-Beyond trial. Most worrying was the disclosure of four new venous thromboembolic events (VTEs), coming on top of the two that had earlier

sounded the first note of caution over the Jak class (*Therapy focus – Atopic dermatitis competition Jaks up, September 14, 2017*).

Leerink analysts painted a bleak picture, suggesting that it was no longer possible to dismiss this as background noise. The phase III VTE rate is now 16.3 per 1,000 patient years of exposure, well above the 3-8 rate expected for RA, they wrote, calling this “a clear signal about [upadacitinib’s] pro-thrombotic activity”.

Of course, it is not clear to what extent Olumiant would be hit, but the Abbvie data should lead to further scrutiny. Lilly has said that it will resubmit Olumiant by the end of January 2018; the FDA previously asked the company to look into the observed imbalance in VTEs during the placebo-controlled period of its RA clinical trials.

Leerink reckons that if upadacitinib does have a VTE signal, and if Olumiant is delayed further for the same reason, then “it is hard to imagine Gilead’s filgotinib [being] spared from heightened scrutiny, and possibly even class labelling as well”. This class includes other assets from Astellas, Pfizer, Concert and Aclaris.

What's at stake: the Jak inhibitor pipeline

Project	Company	Pharma class	Lead indication(s)	2022e sales ($m)	NPV ($m)	Status
Xeljanz	Pfizer	Jak 3 inhibitor	RA	1,850	10,200	Marketed
Olumiant	Lilly	Jak 1 & 2 inhibitor	RA	670	3,500	Marketed in EU; rejected in US
Upadacitinib/ABT-494	Abbvie	Jak 1 inhibitor	RA, psoriatic arthritis, ulcerative colitis	1,169	6,300	Phase III
Filgotinib	Gilead Sciences	Jak 1 inhibitor	RA, Crohn's disease, ulcerative colitis	245	2,800	Phase III
ASP015K Oral	Astellas Pharma	Jak inhibitor	RA	66	197	Phase III
PF-04965842	Pfizer	Jak 1 inhibitor	Atopic dermatitis	15	102	Phase II
CTP-543	Concert Pharmaceuticals	Jak 1 & 2 inhibitor	Alopecia	114	397	Phase II
ATI-50001	Aclaris Therapeutics	Jak 1 & 3 inhibitor	Alopecia	113	304	Phase I

Souce: EvaluatePharma.

Of this quartet only Astellas’s ASP015K seems to be in trials for RA, however. RA is the most advanced and currently biggest forecast indication for upadacitinib and Olumiant, though this could change given the impressive phase II data the former generated in atopic dermatitis last month.

If there is a silver lining it is that Xeljanz, Pfizer’s marketed Jak inhibitor, seems not to be associated with VTEs, judging by Leerink’s exhaustive review of post-marketing data, and a separate American College of Rheumatology late-breaker looking across phase II and III trials in RA, psoriasis, psoriatic arthritis and ulcerative colitis.

Still, while it cannot be said for sure that this is a class effect, increased monitoring could lead to more VTEs being found, given their frequently asymptomatic nature. Abbvie has shown that this problem is now too widespread to ignore.

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