Evaluate Vantage

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Abbvie vaults first pivotal hurdle with oral RA candidate

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It is highly unlikely that Abbvie will ever be able to find one product capable of filling a Humira-sized hole. Encouraging phase III data on its new rheumatoid arthritis project do at least raise hopes that it has found a decent new contender.

An *EP Vantage* analysis finds that this first pivotal efficacy read out from upadacitinib stacks up very well against other oral RA candidates, although Gilead's filgotinib remains a wild card here (see analysis below). With Eli Lilly hobbled by a surprise FDA rejection, the Jak inhibitor space is still there for the taking.

Of course there is already one such product on the market, Pfizer's Xeljanz; although this made it to the US market in 2012, it has been handicapped by a black box warning of opportunistic infections. It took until March of this year before European regulators were prepared to deem it safe enough for approval.

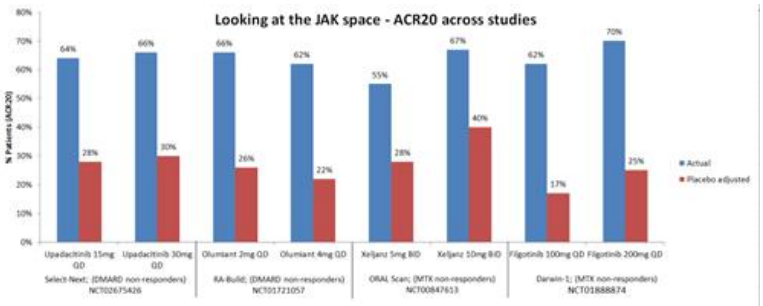
Still, sales are expected to breach the billion dollar mark this year, demonstrating the demand for new products even in such a competitive market.

Lilly's Olumiant is facing the opposite situation – it was approved in Europe this year but knocked back by the FDA. The specific reasons have never been laid out, all Lilly has said is that the complete response letter referred to additional clinical data "needed to determine the most appropriate doses" and to "characterise safety concerns across treatment arms".

Published data on Olumiant do not appear to point to a troubling imbalance of serious adverse events and as far as *EP Vantage* can determine there was no rise in the rate of opportunistic infections across the baricitinib pivotal programme. Rates of these serious life-threatening infections are being closely watched across the Jak trials.

Abbvie did not specifically mention these in the press release yesterday although it did say no new safety findings had been noted. Filgotinib has yet to yield phase III data but no opportunistic infections were reported in its phase IIb Darwin programme.

The concern for Lilly is that the FDA will only approve the lower 2mg dose of Olumiant, which would erase much of its efficacy advantages and remove the ability for patients to titrate down. Still, as the chart below shows, it will have more to worry about if upadacitinib continues to generate such promising results.



Select-Next recruited patients on a stable dose of a disease modifying anti-rheumatic drug (DMARD) but who were failing to respond adequately. As well as hitting the primary endpoint of ACR20, longer-term measures like ACR70 were also successfully achieved, and clinical remission rates of 31% and 28% for the two doses, compared to 10% of placebo patients, make for encouraging reading.

Lilly ran a similar study called RA-Build, also shown here, although the normal caveats of cross-trial comparisons apply. Data from studies of Xeljanz and filgotinib are also shown here for illustrative purposes – results from trials in the DMARD patient population could not be found, and although methotrexate is considered a DMARD it is not considered particularly effective.

As Lilly demonstrated with Olumiant, the devil is in the detail here, and a lot more data on upadacitinib are required to fully assess the project's potential. Abbvie believes that selectively hitting Jak-1 should bestow both safety and efficacy advantages in this space – hence filgotinib is also one to watch.

This asset also hits JAK-1; development partners Galapagos and Gilead started the Finch pivotal programme in

August last year. The first trial, also in patients who have an inadequate response to DMARDs, should yield data in the middle of next year.

By that time, Abbvie will hope to be on its way to regulators. Upadacitinib is looking like a strong asset – albeit with much more data to come – and with Olumiant out of the picture the company has been handed a huge advantage. The pieces are falling into place for Abbvie to make another significant mark, this time in this oral RA space.

Consensus outlook for the Jak market

				Annual Sales WW ($m)	
Company	**Product**	**Pharma class**	**US launch?**	**2017**	**2022**
Pfizer	Xeljanz	JAK 3 inhibitor	2012	1,224	2,188
AbbVie	ABT-494 (upadacitinib)	JAK 1 inhibitor	2019	-	1,214
Eli Lilly	Olumiant	JAK 1 & 2 inhibitor	2020	34	1,085
Gilead/Galapagos	Filgotinib	JAK 1 inhibitor	2020	-	228
Astellas Pharma	ASP015K (peficitinib)	JAK inhibitor	-	-	71
		Total JAK market (incl. others)		*1,258*	*4,791*

Source: EvaluatePharma. Note: Olumiant forecasts still subject to adjustment for CRL

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