Evaluate Vantage

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Tyk2 reaches tipping point

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Bristol-Myers Squibb is ahead in a new oral class that could bring similar efficacy to current injectables for autoimmune diseases – but Pfizer seems less keen.

Never mind the Jak inhibitors. Here are the Tyk2s: a new class of drug from the Jak family that might overcome the safety issues that have plagued older Jaks.

And phase II data last week from the most advanced Tyk2 project, Bristol-Myers Squibb's BMS-986165, suggest that on efficacy the compound could rival – or even beat – existing psoriasis therapies. Still, not everyone seems convinced. In alopecia Pfizer has chosen a Jak3 inhibitor over its Tyk2 and Jak1 blocker PF-06700841, despite apparently better efficacy with the latter in a trial that included both agents.

Similar studies of PF-06700841 and PF-06651600 in Crohn's and ulcerative colitis should read out in the next couple of years; if Pfizer keeps picking the more selective Jak3 agent doubts could creep in about the Tyk2 mechanism.

But, with no suggestion that safety was an issue with either asset, perhaps Pfizer is simply trying to carve out a niche for its Jak3 inhibitor in the underserved alopecia indication, and has bigger plans for its Tyk2 inhibitor.

Bristol and Pfizer are not the only big players making a bet on Tyk2. Johnson & Johnson is partnered with Theravance on TD-1473, which should go into phase II/III development this year, while Celgene has an option on Nimbus Therapeutics' preclinical Tyk2 programme. The much smaller UK company Sareum is also involved, recently naming a preclinical autoimmune disease candidate, SDC-1801.

The TYK2 pipeline			
Project	**Company**	**Target**	**Clinical programme**
Clinical assets			
BMS-986165	Bristol-Myers Squibb	Tyk2	Psoriasis (phase III); lupus, Crohn's (phase II)
PF-06700841	Pfizer	Tyk2; Jak1	Ulcerative colitis, Crohn's, alopecia, psoriasis (phase II)
TD-1473	J&J/Theravance	Tyk2; Jak1; Jak2; Jak3	Crohn's (phase II)
PF-06826647	Pfizer	Tyk2	Psoriasis (phase I)
Notable preclinical assets			
SDC-1801	Sareum	Tyk2; Jak1	-
TYK2 programme	Nimbus (Celgene has option)	Tyk2	-
Abandoned in the clinic			
JAK1/TKY2 Inhibitor	Pfizer	Tyk2; Jak1; Jak2; Jak3	-
PF-06263276	Pfizer	Tyk2; Jak1; Jak2; Jak3	-
Tyk2/JAK1 Research Project	Pfizer	Tyk2; Jak	-
Source: EvaluatePharma.			

But Bristol is out in front, having already started pivotal trials in psoriasis before the readout from its phase II study, which came last week at the European Academy of Dermatology and Venerology (EADV) congress in Paris.

The results explained why Bristol had been so keen to push into phase III: the data made BMS-986165 look more effective than Celgene's oral psoriasis drug Otezla, and comparable to some injectables.

In the phase II trial 75% of patients receiving the highest 12mg dose of BMS-986165 achieved PASI-75, a 75% reduction in the psoriasis area and severity index score. The proportion of Otezla-treated patients reaching PASI-75 in the phase III Esteem 1 trial was just 33%. However, the usual caveats about cross-trial comparisons apply.

Bristol is obviously confident of beating Otezla, and is pitting BMS-986165 against the Celgene drug in its two phase III trials, POETYK-PSO-1 and POETYK-PSO-2, which are due to complete in 2020.

Still, with Otezla seen as a less effective but safer alternative to biologicals, the bigger test for BMS-986165, if approved, will be against injectables like Abbvie's Humira. Perhaps Bristol believes that the convenience of an oral molecule could help it grab market share.

Safety first

Promising data aside, the Tyk2s still have a lot to prove, and their safety will be closely watched. Currently approved Jak inhibitors such as Pfizer's Xeljanz and Lilly's Olumiant carry black box warnings for serious infections, and the latter has also been linked with thrombosis.

The side effects are thought to be due to these drugs' broad activity across various Jak subtypes, and newer, more selective Jak1 inhibitors such as Galapagos's filgotinib and Abbvie's upadacitinib could avoid these issues. Still, the jury is still out, particularly on the latter.

By not hitting Jak2 and 3, it is thought that Tyk2 inhibitors could also sidestep these adverse events.

Even within the Tyk2s class there might be a trade-off between safety and efficacy, however. There is a theory that the selective Tyk2 inhibitors being developed by the likes of Bristol and Nimbus might sacrifice some

efficacy for safety when compared with the Tyk2/Jak1 inhibitors from Sareum and Pfizer. The latter is hedging its bets with a foot in both camps.

Interestingly, Theravance and J&J's TD-1473 is a pan Jak/Tyk2 inhibitor, but is thought to act locally in the gut with minimal systemic absorption, which could reduce potential for side effects – explaining why it is only being investigated in inflammatory bowel diseases.

Pfizer, which has gone big on Tyk2, has discontinued a couple of less selective Jak/Tyk inhibitors. It is unclear whether this was down to safety reasons, but this seems a logical conclusion.

I'd rather Jak

With a lot of experience in this arena, Pfizer presumably knows what it is doing. So it was surprising to see the company ditch PF-06700841 in alopecia in favour of its Jak3 inhibitor, PF-06651600 – despite the Tyk/Jak1 inhibitor showing a 49.5-point reduction in the severity of alopecia tool (SALT) versus the Jak3 inhibitor's 33.6-point reduction.

The data were also presented at the EADV meeting over the weekend.

More trials of the two drugs in Crohn's and ulcerative colitis are set to complete in 2020 – Pfizer pointed out that these are not head-to-head studies and the agents are being compared with placebo. Perhaps Pfizer is keeping its Tyk2 powder dry for these potentially more lucrative indications. Alopecia, although currently untreatable, is seen as a superficial disease, although the company talked up the "profound psychological consequences" associated with it.

Perhaps Pfizer just wants to command separate niches for its various Jaks and Tyks, allowing them to be priced differently in separate indications.

PF-06700841 is also still in play in psoriasis, where it completed a phase II trial earlier this year. Results from that study will no doubt be compared against the BMS-986165 trial, and could give an early clue about the safety/efficacy trade-offs between the more and less selective Tyk2 inhibitors.

This story has been updated to reflect the fact that the trials including both PF-06700841 and PF-06651600 are not powered as head-to-head studies.