Evaluate Vantage

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AAD 2023 – Takeda outdoes Bristol’s Sotyktu

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TAK-279 comes out on top in the battle of the Tyk2 inhibitors, but biologicals still rule.

Better efficacy than Bristol Myers Squibb’s Sotyktu, but similar tolerability; that was the long-held aim for the rival Tyk2 inhibitor developed by Nimbus Therapeutics. And the project – now in Takeda’s hands and named TAK-279 – has achieved this in psoriasis, the American Academy of Dermatology meeting heard on Saturday.

But in the phase 2 study TAK-279 did not quite meet the bar set by injectable drugs, which some investors took as a good sign for groups coming behind with other oral options. TAK-279’s $4bn price tag also looms large over Takeda; on a conference call execs denied suggestions that the company had overpaid, but expanding into other indications like inflammatory bowel disease and lupus could be key to the project’s prospects.

First, though, Takeda will have to replicate these findings in phase 3. The group is not giving much away about trial design until it has had discussions with regulators, but hinted that a head-to-head study using a 30mg dose – the highest tested in phase 3 – could be on the cards.

The phase 2 trial tested 2-30mg once-daily doses, with a primary endpoint of the proportion of patients achieving Pasi 75, a 75% improvement in the psoriasis area and severity index.

Cross-trial comparison of TAK-279 and Sotyktu				
	TAK-279 (NDI-034858)			**Sotyktu**
	Ph2*			**Ph3 Poetyk-PSO-1&2****
Endpoint	**5mg**	**15mg**	**30mg**	**6mg**
Pasi 75	38 points	62 points	61 points	44-45 points
Pasi 90	21 points	45 points	46 points	24-32 points
Pasi 100	10 points	15 points	33 points	9-13 points
PGA score 0/1	23 points	45 points	48 points	41-47 points
*Note: all numbers placebo adjusted; TAK-279 trial also included 2mg arm, results not statistically significant vs placebo; *at wk 12; **at wk 16. Source: AAD & Sotyktu label.*				

On this measure, and on a cross-trial basis, the higher doses of TAK-279 looked moderately better than Bristol's Sotyktu, which was approved in psoriasis last year.

But it was the more stringent Pasi 100 – representing clear skin – where TAK-279 really shone. The Takeda execs pointed to results here as "particularly encouraging" in terms of potential differentiation, and noted that achieving clear skin was becoming increasingly important for psoriasis therapies.

However, on both Pasi 75 and 100, TAK-279 fell short of Abbvie's Skyrizi, which has shown rates as high as 89% and 51% respectively.

True, Abbvie's drug is injectable, while TAK-279 is a more convenient oral option. But Stifel analysts argued that the latest results had left "efficacy on the table" for the likes of Ventyx, whose Tyk2 inhibitor VTX958 is set to yield data from the phase 2 Serenity trial in psoriasis in the fourth quarter.

Cross-trial comparison of selected psoriasis agents				
Product/project	**Company**	**Route of admin**	**Trial**	**% of pts meeting Pasi 75**
Sotyktu	Bristol Myers Squibb	Oral	Poetyk-PSO-1	58%*
TAK-279	Takeda (via Nimbus)	Oral	Ph2	67%**
Bimzelx^^	UCB	Subcutaneous	Be Sure	77%^
Cosentyx	Novartis	Subcutaneous	Erasure	82%**
Skyrizi	Abbvie	Subcutaneous	Immhance	89%*
*Note: not placebo-adjusted as some trials used active comparator; TAK-279 data with 30mg dose; Cosentyx data with 300mg dose; *wk 16; **wk 12; ^wk 4; ^^Bimzelx received CRL in May 2022, resubmitted and Pdufa in Q2 2023. Source: AAD, NEJM & product labels.*				

Just as important for Takeda will be TAK-279's safety profile. Here there was nothing too worrying, although the execs said they would be keeping a "close eye on" creatine phosphokinase levels, with elevations seen in some patients. The most common adverse events were Covid infections and acne – and it "remains to be seen" whether the latter is related to Tyk2 inhibition, said Graham Heap, global programme leader at Takeda.

OK or phenomenal?

Overall, based on the phase 2 data, Takeda made much of its potential to have a best-in-class oral molecule – assuming efficacy does not wane too much from phase 2 to phase 3.

However, during Saturday's conference call the Credit Suisse analyst Fumiyoshi Sakai described the psoriasis data as merely "OK" – a description that the Takeda execs refuted.

"We don't think they're OK, we think they're quite phenomenal," said Andy Plump, Takeda's president of R&D. "We've been, for the past eight years, looking for a molecule we'd want to have next to Entyvio in our GI and inflammation portfolio, and this is first one that we made the decision to go after."

But Mr Sakai contended that psoriasis alone did not really justify the $4bn investment.

“Did we pay a lot for this asset? I would say no,” said Uthra Sundaram, Takeda’s head of global product and launch strategy. She also highlighted the group’s plans in IBD, where phase 2 trials are set to start this year; notably, Sotyktu previously failed in ulcerative colitis. In IBD, Mr Heap said Takeda would explore a range of TAK-279 doses.

Across all the indications a “guiding principle” will be speed, Mr Plump said. “We’re ready to push this programme very quickly. It’s our top priority in R&D right now.”