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Therapy focus – Atopic dermatitis competition Jaks up

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The launch of Sanofi and Regeneron's atopic dermatitis therapy Dupixent has been slower than some had expected, but hopes are still high for the product. However, several mid-stage assets could start putting some unwelcome pressure on the anti-IL-4 & IL-13 MAb in the not-too-distant future (see table below).

One of these potential rivals is Abbvie's Jak inhibitor upadacitinib, which last week posted phase IIb data that were impressive enough to hit Regeneron's share price. But thrombotic events are a worry with Jaks, and upadacitinib has not escaped these issues – this could throw a spanner in the works for Abbvie and play in Sanofi and Regeneron's favour.

Until Dupixent's approval in March there were few options available for the more severe end of the atopic dermatitis spectrum, which explains the enthusiasm from the sellside. Still, the product has a lot of catching up to do to meet its $181m sales forecast this year, with second-quarter revenues of €26m ($31m) falling short of analyst expectations and leaving it needing to ramp up significantly in the second half.

Top five eczema/dermatitis products in 2022

				Indication sales ($m)			
Product	**Company**	**Mechanism**	**Delivery**	**2016**	**2018**	**2020**	**2022**
Dupixent	Sanofi	Anti-IL-4 & IL-13 MAb	Injected	-	620	2,256	3,625
Eucrisa	Pfizer	PDE4 inhibitor	Topical	-	264	720	1,118
Bepanthen	Bayer	Vitamin B5	Topical	400	428	472	496
Temovate	GlaxoSmithKline	Corticosteroid	Topical	102	95	95	95
Cormax	Akorn	Corticosteroid	Topical	70	49	48	47

Source: EvaluatePharma.

Upadacitinib is being tested in a similar population to Dupixent's approved indication: patients with moderate to severe disease who have an inadequate response to topical steroids. If it can sidestep the safety issues it has a chance to grab a chunk of this market.

There are not too many late-stage candidates to challenge Dupixent in the near term: the only novel projects in phase III, according to an *EP Vantage* analysis, are the similarly acting anti-IL-13 MAb tralokinumab – which Astrazeneca licensed to Leo Pharma in dermatology indications – Amorepacific's transient receptor potential vanilloid (TRPV) 1 antagonist PAC-14028, and Japan Tobacco's topical Jak inhibitor JTE-052, which is in trials in Japan.

However there are nine active projects in phase II. Lilly's Olumiant, which has been knocked back by the FDA in rheumatoid arthritis, has just posted positive phase II results, but only at the higher dose studied. Lilly says it plans to start phase III development in atopic dermatitis later this year.

Atopic dermatitis candidates in active clinical trials					
Project	**Company**	**Description**	**Enrolment**	**Trial ID**	**Prima compl date**
Phase III					
PAC-14028	Amorepacific	TRPV 1 antagonist	240	NCT02965118	Aug 20
Tralokinumab	Astrazeneca/Leo Pharma	Anti-IL-13 MAb	780/780	NCT03160885/NCT03131648	Nov 2019/F 2020
JTE-052	Japan Tobacco/Torii Pharmaceutical	Topical Jak inhibitor	150/330	JapicCTI-173554/JapicCTI-173555	Unkno
Phase II					
ABT-494/upadacitinib	Abbvie	Jak 1 inhibitor	167	NCT02925117	Report
Olumiant	Lilly/Incyte	Jak 1& 2 inhibitor	124	NCT02576938	Report
Lebrikizumab	Dermira	Anti-IL-13 MAb	N/A	N/A	Phase start
INCB018424 Phosphate Cream	Incyte	Topical Jak 1 & 2 inhibitor	300	NCT03011892	Jul 201
DMT210	Dermata Therapeutics	GPCR antagonist	25	NCT02949960	Aug 20
FURESTEM-AD	Kang Stem Biotech	Stem cell therapy	206	NCT03269773	Dec 20
ALX-101	Ralexar Therapeutics	LXR agonist	203	NCT03175354	Dec 20
Cosentyx	Novartis	Anti-IL-17 MAb	44	NCT02594098	Apr 20
Nemolizumab	Chugai Pharmaceutical/Roche	Anti-IL-31 MAb	250	NCT03100344	Jun 20
Source: clinicaltrials.gov; EvaluatePharma.					

Another project no longer in the hands of big pharma is the anti-IL-13 MAb lebrikizumab, developed by Roche but licensed to Dermira for dermatology indications. A Roche-sponsored study is listed as completed, and Dermira has said it plans to start a phase IIb trial in the near future.

It is interesting that both Astra and Roche have opted to leave this sector – this might have something to do with failures with both lebrikizumab and tralokinumab in asthma, an indication where Dupixent is still active (*Regeneron and Sanofi breathe easier on Dupixent, September 11, 2017*).

Or perhaps they want to avoid a fight with Dupixent, which by then will have had plenty of time to establish itself. Smaller players, meanwhile, might believe that they can still find a relatively lucrative niche.

Risk-benefit

However, Abbvie is unlikely to be satisfied with upadacitinib being an also-ran, even in one of its follow-on indications. Expectations for the project, also known as ABT-494, in atopic dermatitis are low; its entire $1.2bn 2022 *EvaluatePharma* sellside consensus forecast comes from its lead indication, rheumatoid arthritis.

This could change after the Jak inhibitor posted a phase IIb win last week. The trial met its primary endpoint of mean percentage change in eczema area and severity index (EASI) score at 16 weeks at all doses studied, with a clear dose response.

The data appear to put the higher doses of upadacitinib in line with Dupixent in terms of efficacy, although the usual caveats about across-trial comparisons apply.

Upadacitinib vs Dupixent								
	Upadacitinib phase IIb				Phase III – Solo 1		Phase III – Solo 2	
	Placebo	7.5mg	15mg	30mg	Placebo	Dupixent every other week	Placebo	Dupixent every other week
# of patients	41	42	42	42	224	224	236	233
Mean percentage change in EASI score†	23%	39%***	62%*	74%*	38%	72%*	31%	67%*
IGA score of 0 or 1‡	2%	14%***	31%*	50%*	10%	38%*	8%	38%*
*†Primary endpoint in upadacitinib trial; ‡Primary endpoint in Solo 1 & 2: proportion of patients with both IGA 0-1 and a reduction from baseline of ≥2 points at week 16; *p<0.001 **p<0.01 ***p<0.05; Source: Leerink note September 7, 2017.*								

Abbvie will advance upadacitinib into phase III studies in atopic dermatitis in 2018. However, safety will be closely watched, following concerns about thrombotic events with other Jak inhibitors including Lilly's Olumiant and Pfizer's Xeljanz (*Olumiant clot signal echoes Xeljanz experience, July 26, 2017*).

These did not appear to be a problem with upadacitinib in the atopic dermatitis trial: according to Abbvie there were no new safety signals and no cases of pulmonary embolism or deep vein thrombosis.

However, this week the company reported two deaths in a phase III trial in RA, Select-Beyond: one due to an unknown cause, and the other due to heart failure presumed related to pulmonary embolism. There was also a non-fatal case of pulmonary embolism, but no episodes of deep vein thrombosis. Its first pivotal RA study, Select-Next, did not raise any serious safety concerns and Abbvie maintains that the rate of pulmonary embolism seen with upadacitinib is consistent with the background rate in the RA patient population. But the issue will no doubt be closely watched in the several ongoing phase III RA trials, as well as the pivotal atopic dermatitis study.

Whatever happens with upadacitinib, the potential seen in atopic dermatitis means other rivals will emerge. Sanofi in particular is heavily reliant on Dupixent; the product's net present value accounts for 16% of the French group's market cap.

Last week's wobble – when Regeneron's shares fell 6% on the upadacitinib data – shows just how important it is that Dupixent delivers. With so much at stake, the companies will hope that competition holds off for a little longer.

Project	Study	Trial ID	Data
Upadacitinib	Phase IIb trial in atopic dermatitis	NCT02925117	Reported
Upadacitinib	Select-Next (RA)	NCT02675426	Reported
Upadacitinib	Select-Beyond (RA)	NCT02706847	Reported
Upadacitinib	Select-Compare (RA)	NCT02629159	Primary completion Aug 2017
Upadacitinib	Select-Monotherapy (RA)	NCT02706951	Primary completion Oct 2017
Upadacitinib	Select-Early (RA)	NCT02706873	Primary completion Jul 2018
Upadacitinib	Select-Choice (RA)	NCT03086343	Primary completion Jul 2019

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