Incremental risk of adverse events with oral Janus kinase inhibitor use in atopic dermatitis and other indications: a systematic review and meta-analysis

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Objective

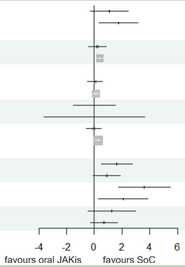
- To estimate the incremental risk of pre-specified adverse events (AEs) per patient-year of oral JAKis compared with standard of care, including topical corticosteroids, biologic agents, and other treatments, among patients with atopic dermatitis or with other diagnoses

Results

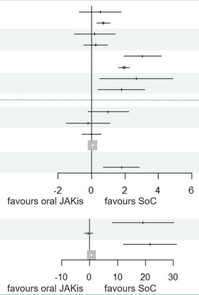
Adverse events

Figure 1. Incidence rate differences of AEs comparing JAKis vs standard of care

Outcome category	Adverse event	Population	JAKi: cases / PY	SoC: cases / PY	IRD	95% CI	NNH
Serious adverse events	Serious adverse events	AD	164 / 2597	80 / 1466	1.07	(-0.31; 2.45)	94
		Non-AD	1537 / 18526	642 / 9289	1.73	(0.31; 3.15)	58
Oncological	Malignancies	AD	10 / 1669	3 / 953	0.22	(-0.41; 0.86)	452
		Non-AD	238 / 16861	74 / 8895	0.40	(0.15; 0.64)	254
CV and thromboembolic	MACE	AD	2 / 1739	0 / 971	0.04	(-0.50; 0.58)	2388
		Non-AD	124 / 14889	55 / 8199	0.12	(-0.11; 0.35)	809
	Thromboembolic events	AD	0 / 181	0 / 127	0.00	(-1.54; 1.54)	-
		Non-AD	0 / 95	0 / 70	0.00	(-3.62; 3.62)	-
	VTEs	AD	0 / 1351	1 / 913	-0.04	(-0.58; 0.50)	-2545*
		Non-AD	75 / 13669	22 / 7017	0.27	(0.09; 0.45)	372
Hematological	Anemia	AD	34 / 1280	6 / 750	1.63	(0.50; 2.75)	62
		Non-AD	338 / 15510	138 / 7981	0.89	(-0.10; 1.88)	113
	Neutropenia	AD	49 / 873	5 / 545	3.62	(1.74; 5.49)	28
		Non-AD	98 / 2404	38 / 1357	2.08	(0.29; 3.87)	49
	Thrombocytopenia	AD	10 / 456	1 / 273	1.25	(-0.47; 2.97)	81
		Non-AD	3 / 479	1 / 449	0.69	(-0.30; 1.67)	146



Outcome category	Adverse event	Population	JAKi: cases / PY	SoC: cases / PY	Incidence Rate Difference	IRD	95% CI	NNH
Infectious disease	Serious infections	AD	40 / 1731	15 / 777		0.52	(-0.74; 1.78)	193
		Non-AD	526 / 17809	201 / 9008		0.71	(0.31; 1.10)	142
	Serious and opportunistic viral infections	AD	6 / 662	4 / 367		0.18	(-1.03; 1.40)	547
		Non-AD	1 / 537	0 / 433		0.25	(-0.45; 0.95)	402
	Herpes zoster	AD	98 / 2367	16 / 1213		3.05	(1.94; 4.17)	33
		Non-AD	607 / 19099	111 / 10014		1.95	(1.63; 2.27)	52
	URTIs	AD	347 / 1946	139 / 1127		2.67	(0.48; 4.85)	38
		Non-AD	1366 / 16681	574 / 8338		1.79	(0.40; 3.18)	56
GI and metabolic	Diarrhea	AD	82 / 1401	23 / 603		1.00	(-0.21; 2.22)	100
		Non-AD	428 / 15904	205 / 7812		-0.20	(-1.51; 1.11)	-494*
	GI perforation	AD	0 / 1564	0 / 851		0.00	(-0.57; 0.57)	-
		Non-AD	22 / 13428	5 / 7396		0.06	(-0.04; 0.16)	1563
	Hyperlipidaemia	AD						
		Non-AD	91 / 1619	30 / 1034		1.79	(0.70; 2.88)	56
Other	Nausea	AD	229 / 1134	27 / 668		19.06	(8.08; 30.05)	6
		Non-AD	465 / 16293	216 / 7943		-0.27	(-1.72; 1.17)	-365*
	Acne	AD	377 / 1502	39 / 909		21.63	(12.15; 31.11)	5
		Non-AD	15 / 1571	0 / 373		0.65	(0.10; 1.21)	153



*indicating higher risk in SoC compared to oral JAKis

Summary

Table 1. NHH, summary results

Category	AE	NNH in AD	NNH in non-AD
Oncological outcomes	Malignancies	452	254
Cardiovascular and thromboembolic outcomes	MACE	2388	809
	Thromboembolic events	–[a]	–[a]
	VTE	-2545[b]	372
Hematological outcomes	Anemia	62	113
	Neutropenia	28	49
	Thrombocytopenia	81	146
Infectious disease outcomes	Serious infections	193	142
	Serious & opportunistic viral infections	547	402
	Herpes zoster	33	52
	URTIs	38	56
Gastrointestinal and metabolic outcomes	Nausea	6	-365[b]
	Diarrhoea	100	-494[b]
	Gastrointestinal perforation	–[a]	1563
	Hyperlipidemia	–[c]	56
Serious adverse events	Serious adverse events	94	58
Dermatological outcomes	Acne	5	153

[a]Zero events for all identified trials in both arms: oral JAKis and SoC; [b]Indicating higher risk in SoC compared to oral JAKis; [c]none of identified studies reported results for this endpoint.

Conclusions

- The M-A identified an increased risk with oral JAKis compared with SoC for multiple AEs, spanning from less to more severe AE, including malignancies in both AD and non-AD populations
- As safety risks are observed in both the AD and non-AD populations, the use of oral JAKis should be carefully considered

Background

- The number of treatment options for patients with moderate-severe atopic dermatitis (AD) is increasing, however their safety profiles vary
- The safety profile of oral Janus kinase inhibitors (JAKis) remains a concern, and the main safety outcomes of the ORAL surveillance study are considered class effects of all oral JAKis by EMA[1,2]
- Type 2 cytokines are critical components of AD pathogenesis and their overexpression leads to barrier defects and inflammation JAKis can interfere with the signaling pathways of some type 2 cytokines, in addition to cytokines and growth factors of other inflammatory pathways related to diseases such as rheumatoid arthritis[3]
- Safety warnings for these products have combined data across indications, making it difficult to assess risk for specific populations

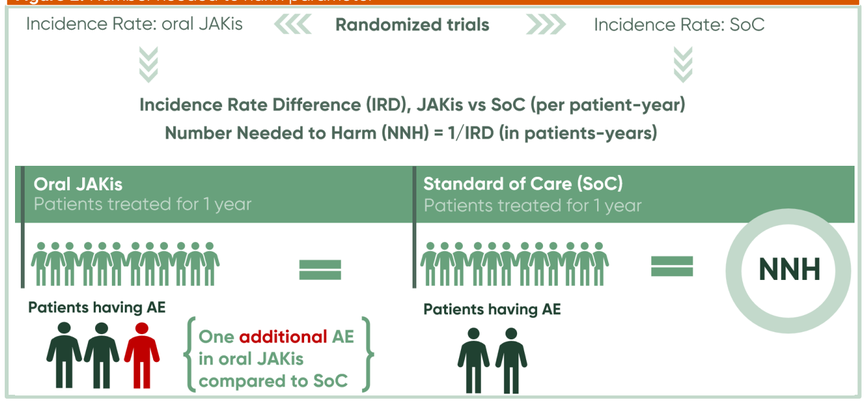
Abbreviations

AD, atopic dermatitis; AE, adverse events; CI, confidence interval; CV, cardiovascular; EMA, European Medicines Agency; GI, gastrointestinal; IRD, incidence rate difference; JAKis, janus kinase inhibitors; MA, meta-analyses; MACE, major adverse cardiac events; NNH, number needed to harm; OLE, open-label extension; PICOS, population, intervention(s), comparator(s), outcomes, study design; PY, patient-years; RCT, randomized controlled trial; SLR, systematic literature review; SOC, standard of care; UTRI, upper respiratory tract infection; VTE, venous thromboembolism.

Methods

- A systematic literature review (SLR) was conducted on 17 preselected AEs [1] based on randomized controlled trials of oral JAKis in AD and non-AD indications
- Meta-analyses (MA) estimated the incidence rate difference (IRD) for each AE between oral JAKis and standard of care (SoC)*, both in AD and non-AD populations
- Number needed to harm (NNH) was calculated as the inverse of the IRD for each AE (**Figure 2**)
  - * Including monoclonal antibodies, tumor necrosis factor inhibitors, antimetabolites, selective T cell co-stimulation modulators, topical corticosteroids, disease-modifying antirheumatic drugs and stable background therapies (glucocorticoids)

Figure 2. Number needed to harm parameter



Systematic Literature Review

- Identification: records identified through database search (n=5618)
- Screening: records screened (n=5601)
- Eligibility: full-text articles assessed for eligibility (n=393)
- Inclusion: articles included (n=109, including n=21 for AD indication) (**Table 2**)

Table 2. SLR PICOS criteria

PICOS	Inclusion criteria
	Initial search
Population	Immunology-mediated diseases: atopic dermatitis, psoriasis, psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, crohn's disease, chronic hand eczema, ankylosing spondylitis, axial spondyloarthritis, hidradenitis suppurativa, alopecia areata
Intervention(s)	**Orally administered: baricitinib, abrocitinib, upadacitinib, tofacitinib**
Comparator(s)	No restrictions
Outcomes	Incidence of AEs: • serious AEs • serious infections • venous thromboembolism events • herpes zoster • upper respiratory tract infection • hyperlipidaemia • acne • nausea • diarrhea • serious and opportunistic viral infections • thromboembolic events • MACE • malignancies • haematological abnormalities • GI perforation
Study design	RCTs (with parallel or cross-over designs and OLE reported as secondary reference to RCTs)

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References

1. Janus Kinase inhibitors (JAKi) Article-20 procedure - European Medicines Agency. (2022). Retrieved 20 July 2023, from https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki. **2.** Janus Kinase inhibitors (JAKi) Article-20 procedure – Annex - Scientific conclusions (2023). Retrieved 20 July 2023, from https://www.ema.europa.eu/en/documents/referral/janus-kinase-inhibitors-jaki-article-20-procedure-annex-scientific-conclusions_en.pdf. **3.** Solas, A., Hernandez-Rocha, C., Duijvestein, M. et al. JAK–STAT pathway targeting for the treatment of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 17, 323–337 (2020).

Disclosures

Shannon Schneider, Lasse Ryttig and Henrik Brandi are employees of LEO Pharma. **Mateusz Nikodem, Malgorzata Panek,Magdelana Damentko and Kamila Chudzik** are employees of Putnam PHMR which received funding from LEO Pharma to conduct the study. However, the funding did not influence the design, conduct, or reporting of the research presented in this poster.

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