Joining the conversation on our evolving understanding of psoriasis and PsA management strategies: IL-23 pathway inhibition

Learnings from the Janssen-Sponsored Hybrid Satellite Symposium at the 9th Psoriasis: from Gene to Clinic Congress on 10 December 2021

With speakers:

Professor Bruce Kirkham and Dr Kave Shams

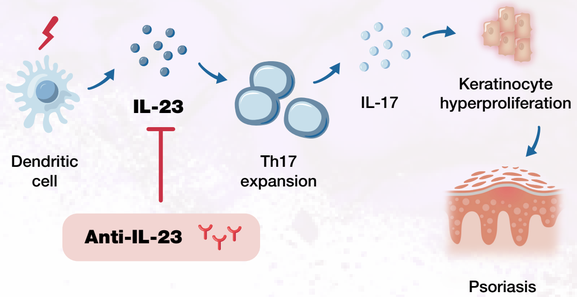
Janssen Immunology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

1 What IL-23 inhibition means for the management of psoriasis

IL-23 has a key role in the development of psoriasis

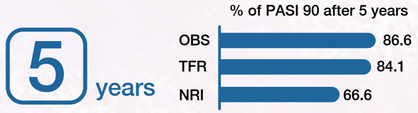
Current model of psoriasis immunopathogenesis:

Release of **IL-23** from dendritic cells following environmental stress triggers induces Th17 cell differentiation, resulting in **elevated IL-17 secretion** and **pathological responses in keratinocytes**[1, 2]

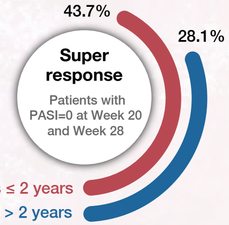


IL-23 efficacy and treatment timing

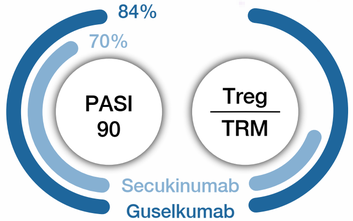
Data from the VOYAGE-1 phase 3 clinical trial showed that **Guselkumab** leads to **sustained PASI 90 response** through **5 years**[3]



Week 28 data from the phase 3b GUIDE study shows **patients with a SDD** were more likely than patients with a LDD to **achieve complete skin clearance faster** and at a higher rate following guselkumab treatment[4]



IL-23 vs IL-17, Treg/TRM



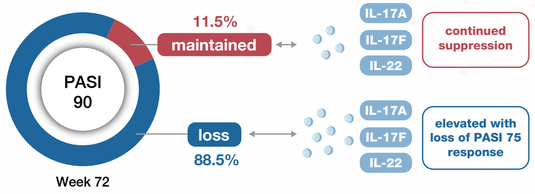
Improved PASI 90 response with guselkumab treatment compared to secukinumab at **week 48** of the ECLIPSE trial[5]

Flow cytometric analysis of skin biopsies from patients in the ECLIPSE trial showed **blockade of IL-23 leads to an increased ratio of Treg/TRM** at **Week 24** of treatment[6]

Increased Treg/TRM ratio observed with guselkumab compared with that observed with secukinumab by **week 24** may be related to the **superior long-term control of skin inflammation** with guselkumab observed at **week 48**[5,6]

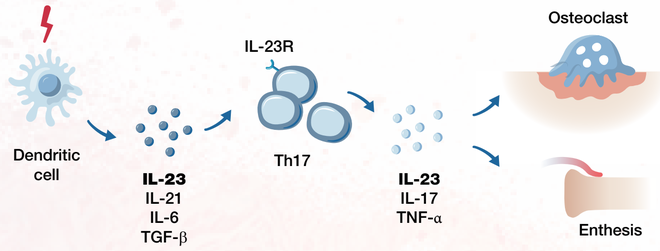
Guselkumab withdrawal[7]

- Data from the phase 3 VOYAGE 2 clinical trial showed **11.5%** of patients **maintained PASI 90 response at Week 72** following guselkumab withdrawal at Week 28
- **Maintained PASI 90 response** following guselkumab withdrawal is associated with continued **IL-17A/F** and **IL-22 suppression**



2 PsA and the role of the IL-23 pathway

IL-23 is a key upstream regulator in PsA[8]

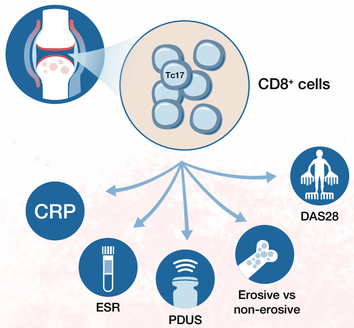


Genetic variants within certain genes have been found to be associated with PsA and psoriasis[9, 10]

	Psoriasis	PsA
T-cell signalling genes	*IL-2, IL-21, IL-12B, IL-13, **IL-23A, IL-23R***	
	ZNF313	

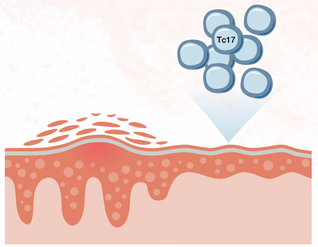
IL-17 cells in synovial fluid

IL-17 producing CD8⁺ cells are elevated in synovial fluid of PsA patients, showing **high correlation with disease activities**[11]



TRM

In psoriasis, **CD8⁺ TRM cells with IL-17A-producing potential** accumulate in non-lesional psoriasis sites, and possibly **correlate with disease duration**[12]



IL-23 efficacy in PsA

Blockade of the IL-23 pathway with **guselkumab** may result in **significant improvements in ACR 50 responses** in:

TNFi-experienced patients (DISCOVER-1 trial)[13]

Biologic-naïve patients (DISCOVER-2 trial)[14]

Increased baseline levels of **IL-23/Th17 cytokines** in PsA patients in DISCOVER studies[15]

- Both guselkumab and ustekinumab lead to reduced IL-17 serum levels at Week 4, with guselkumab further reducing IL-17 levels at Week 24 whilst ustekinumab does not[15,16]
- This suggests **IL-23 blockade may more deeply suppress IL-17** compared to IL-12/23 inhibition[15]

Abbreviations: ACR 50, ≥ 50% improvement in American College of Rheumatology response; **CD**, cluster of differentiation; **CRP**, C-reactive protein; **DAS28**, 28-point rheumatoid arthritis-specific disease activity score; **ESR**, erythrocyte sedimentation rate; **IL**, interleukin; **LDD**, long disease duration; **NRI**, non-responder imputation; **OBS**, as observed method; **PASI 90**, ≥ 90% improvement in Psoriasis Area and Severity Index response; **PDUS**, power Doppler ultrasound; **PsA**, psoriatic arthritis; **SDD**, short disease duration; **Tc17 cell**, IL-17-producing CD8⁺T cell; **TFR**, treatment failure rules method; **Th17 cell**, IL-17-producing CD4⁺ cell; **TNF**, tumour necrosis factor; **TNFi**, TNF inhibitor; **Treg**, T regulatory cell; **TRM**, tissue-resident memory T cell; **ZNF**, zinc finger protein.

References: 1. Ten Bergen LL, et al. Scand J Immunol. 2020;92:e12946. **2.** Gooderham MJ, et al. J Eur Acad Dermatol Venereol. 2018;32:1111-9. **3.** Reich K, et al. Br J Dermatol. 2021 Jun 9 [Online ahead of print]. **4.** Schäkel K, et al. Poster presented at ISDS 2021; Abstract 73. **5.** Reich K, et al. Lancet. 2019;394:831-9. **6.** Mehta H, et al. J Invest Dermatol. 2021;141:1707-18.e9. **7.** Gordon KB, et al. J Invest Dermatol. 2019;139:2437-46.e1. **8.** Veale DJ, Fearon U. Lancet. 2018;391:2273-84. **9.** Hébert HL, et al. Br J Dermatol. 2012;166:474-82. **10.** Nograles KE, Krueger JG. Exp Cell Res. 2011;317:1293-300. **11.** Menon B, et al. Arthritis Rheumatol. 2014;66:1272-81. **12.** Vo S, et al. Br J Dermatol. 2019;181:410-2. **13.** Ritchlin CT, et al. RMD Open. 2021;7:e001457. **14.** McInnes IB, et al. Poster presented at EULAR 2021; POS1027. **15.** Sweet K, et al. RMD Open. 2021;7:e001679. **16.** Siebert S, et al. Arthritis Rheumatol. 2019;71:1660-9.

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