Reduction of Skin CD8 TRMs in Icotrokinra-Treated Participants With Moderate-to-Severe Plaque Psoriasis: Phase 3 ICONIC-LEAD Results Through Week 52

J. Angsana,[1] Y. Ren,[1] J. Sendecki,[2] K. Kohler,[1] N. Roscoe,[1] J. Gooco,[1] C. Sisk,[2] T. Lee,[2] C. DeKlotz,[2] M. Miller-Kassamali,[2] J. Cafone,[2] P. Newbold,[2] A. Kannan,[2] M.E. Polak,[2] D. Waterworth,[2] N. Sabins,[2] C. Cuff,[3] K. Eyerich,[4] K. Wolk,[5] R. Sabat,[5] H. Mehta,[6] M. Sarfati,[6] S. Molin,[5] R. Bissonnette[7]

[1]Johnson & Johnson, San Diego, CA, USA; [2]Johnson & Johnson, Spring House, PA, USA; [3]Johnson & Johnson, Cambridge, MA, USA; [4]University of Freiburg, Freiburg, Germany; [5]Charité-Universitätsmedizin Berlin, Berlin, Germany; [6]Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; [7]Innovaderm Research, Montreal, QC, Canada

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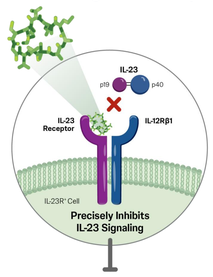
Background

Plaque psoriasis (PsO) is a chronic inflammatory skin disease in which dysregulation of interleukin (IL)-23 activation plays a pivotal role[1]

Icotrokinra (ICO)
- First and only IL-23 receptor (IL-23R)-targeted oral peptide that precisely inhibits IL-23 pathway signaling[2]
- Approved for moderate-to-severe plaque PsO in adults and pediatric patients ≥12 years of age and ≥40 kg[3]

ICONIC-LEAD (NCT06095115)
- Ongoing phase 3 randomized, double-blind, placebo (PBO)-controlled study evaluating the efficacy and safety of once-daily ICO in adults and adolescents with moderate-to-severe plaque PsO[4,5]
- ICO demonstrated higher skin clearance versus PBO at Week (W)16, with responses increasing through W24[4]
- Adults continuing ICO demonstrated superior maintenance of skin response (Psoriasis Area and Severity Index [PASI] and Investigator's Global Assessment [IGA]) from W24-52 versus those withdrawn to PBO; in adolescents, ICO showed high and durable skin clearance through W52[5]
- ICO adverse event rates were similar to PBO through W16, and did not increase through W52

Icotrokinra Blocks IL-23 From Binding to its Receptor



Inhibits IL-17A, IL-17F, and IL-22 Production

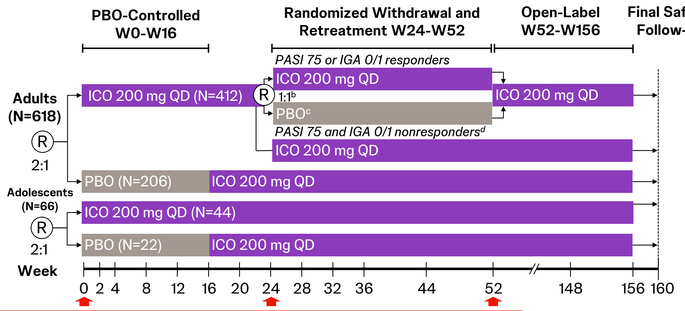
IL-12Rβ1=interleukin-12 receptor beta 1.

Objective

Evaluate ICO pharmacodynamic (PD) effects on skin epidermal thickness and T cell densities/cell counts through W52 among adult and adolescent participants with moderate-to-severe plaque PsO in ICONIC-LEAD

ICONIC-LEAD – Study Design and Skin Sample Analysis[a]

Key inclusion criteria
- ≥12 years
- Plaque PsO for ≥26 weeks
- BSA ≥10%
- PASI score ≥12
- IGA score ≥3
- Candidate for phototherapy or systemic treatment for plaque PsO



Skin Samples	Histology/H&E	ICO N= 28 LS / 28 NLS	28 LS	15 LS
		PBO→ICO N= 16 LS / 16 NLS	16 LS	12 LS
	Immunofluorescence (IF)	ICO N= 32 LS / 32 NLS	32 LS	18 LS
		PBO→ICO N= 18 LS / 18 NLS	18 LS	15 LS
	Flow cytometry (FC)	ICO N= 12 LS / 12 NLS	8 LS	6 LS
		PBO→ICO N= 4 LS / 4 NLS	4 LS	4 LS

*[a]In a subset of consenting participants. [b]At W24, adults who were PASI 75 or IGA score of 0 or 1 responders were rerandomized to continue ICO or PBO. [c]W24 ICO responders rerandomized to PBO at W24 were excluded from W52 biomarker analyses shown here. [d]W24 ICO non-responders and adolescents were included in W52 biomarker analyses shown here. **BSA**=body surface area, **H&E**=hematoxylin and eosin, **LS**=lesional skin, **NLS**=non-lesional skin, **QD**=daily, **R**=randomized.*

Assessments and Analysis

Assessments	Analysis
Skin epidermal thickness • Histological analysis using H&E staining[a]	• LS vs NLS at W0: • One-sample t-tests of log_2 fold change between NLS and LS at W0
T cell densities • Assessed using IF[a,b,c]: • CD3 T cells • CD8 TRMs ($CD3^+CD8^+CD103^+$)	• Linear mixed effects modeling of: • W24 and W52 log_2 fold change from W0 LS as associated with treatment group[e] • Marginal mean estimates of change from baseline were derived, with corresponding 95% CIs
T cell counts • Assessed using FC[b,d]: • CD3 T cells • CD8 TRMs ($CD3^+CD8^+CD103^+$) • IL-17A$^+$ T cells ($CD3^+$IL-17A$^+$) • IL-17F$^+$ T cells ($CD3^+$IL-17F$^+$)	• Linear model of: • Log_2 fold change between NLS and LS at W0 with treatment as a fixed effect • Statistical significance was defined as $p<0.05$

*[a]Assessed using HALO AI v4.0.5107.577 software (Indica Labs). [b]Different sets of skin samples were used for IF and FC. [c]Image analysis was performed using HighPlex FL v4.1.3 algorithm (Indica Labs). [d]Skin cells were isolated through enzymatic (Collagenase type 4 and deoxyribonuclease I) and mechanical digestion process (MACS dissociator). Cells were stained with extracellular and intracellular antibodies; counting beads were included in a separate counting panel to calculate T cell numbers per biopsy. Data were analyzed using FlowJo v10.10.0 (FlowJo). [e]Adjusted for W0 levels, interaction between time and treatment, participant random effect, among other covariates. **CI**=confidence interval, **TRM**=tissue-resident memory T cell.*

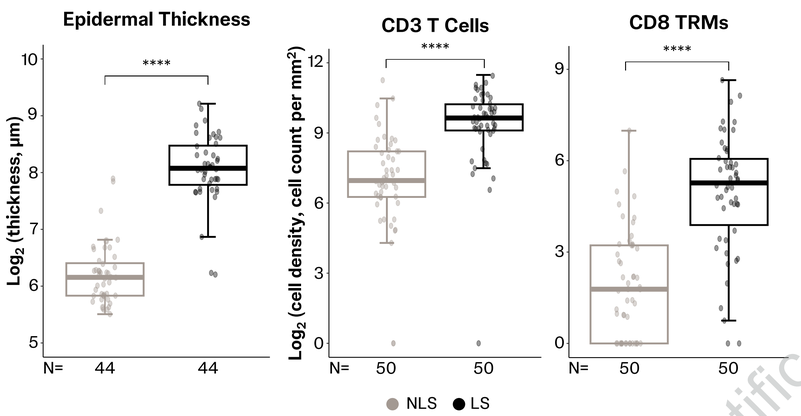
Key Takeaways

- **In the phase 3 ICONIC-LEAD study of adults and adolescents with plaque PsO, ICO robustly and durably reduced biomarkers implicated in PsO pathogenesis**
  - ✓ **ICO significantly reduced epidermal thickness, T cell densities/cell counts in lesional skin at W24 and W52, with levels approaching non-lesional skin by W52**
  - ✓ **Similar PD effects in lesional skin were seen as early as 8 weeks after W16 transition from PBO→ICO**
- **These cellular changes may, in part, represent the mechanistic basis for the clinical improvement achieved with this first and only IL-23R-targeted oral peptide that precisely inhibits IL-23 pathway signaling**

Results

Epidermal thickness and T cell densities were increased in LS vs NLS at W0

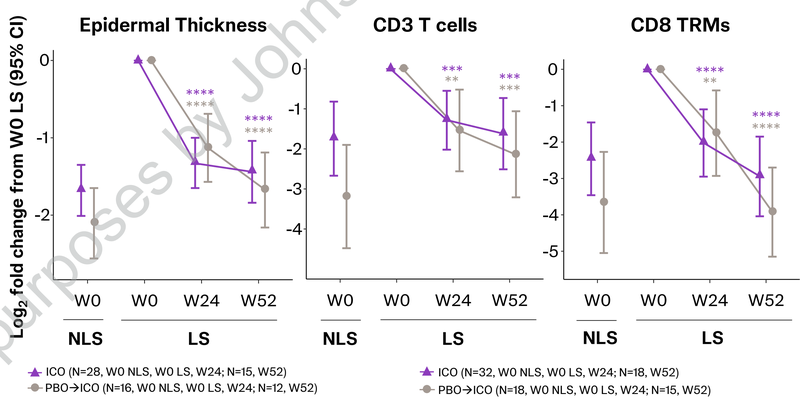
- $CD8^+$ TRMs ($CD3^+CD8^+CD103^+$) that produce IL-17 and are implicated in disease memory, which may contribute to PsO chronicity[6,7], are enriched in PsO LS



*****p<0.0001 for LS vs NLS. Data are presented as Tukey boxplots (median, interquartile range [IQR]; whiskers = 1.5×IQR).*

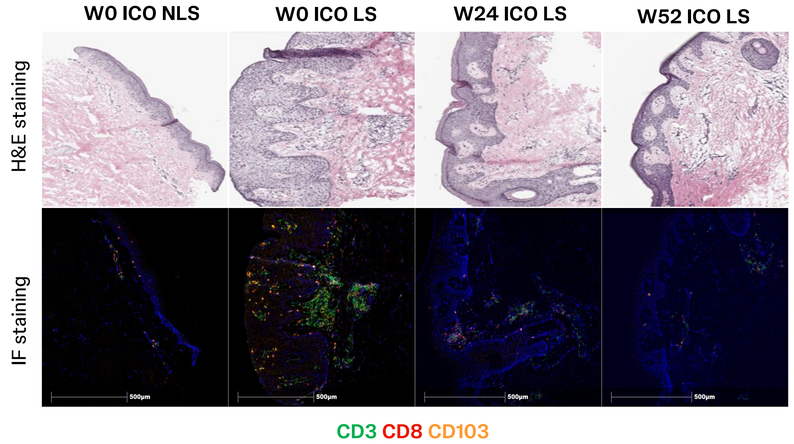
ICO significantly reduced epidermal thickness and T cell densities in LS at W24 and W52 vs W0, with levels approaching NLS at W52

- Epidermal thickness and T cell densities were also significantly reduced as early as 8 weeks after W16 transition from PBO to ICO



***p<0.01, ***p<0.001, ****p<0.0001 for change from W0 LS within treatment group. Points show estimated model mean, whiskers show 95% CIs.*

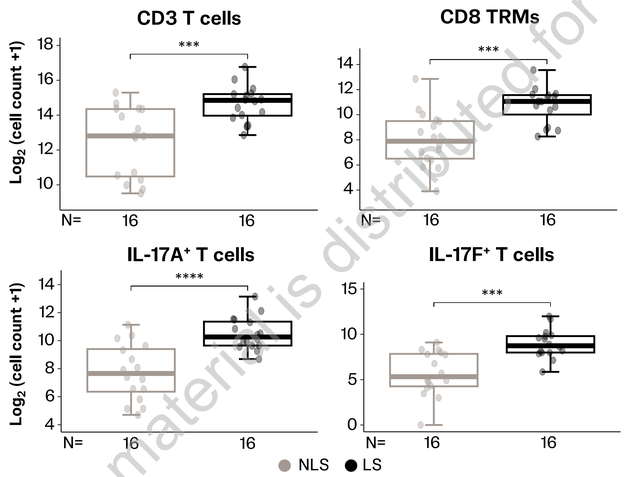
ICO normalized skin architecture and attenuated T cell burden in LS at W24 and W52 vs W0

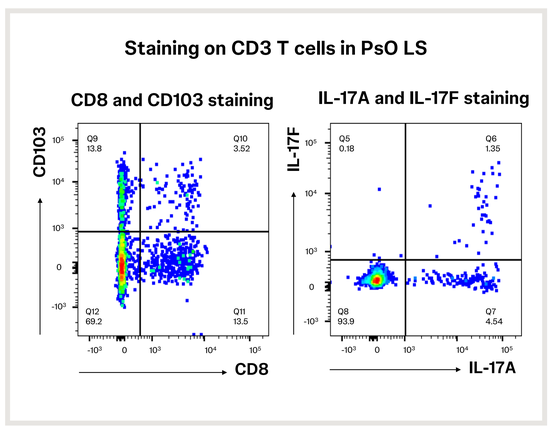


Images shown are representative of ICO-randomized participants who remained on ICO for 52W (N=15).

CD3 T cell, CD8 TRM, IL-17A$^+$ T cell, and IL-17F$^+$ T cell counts were higher in LS vs NLS at W0

- Consistent with IF data, CD3 T cell staining and FC analysis showed expansion of T cell populations in LS at W0

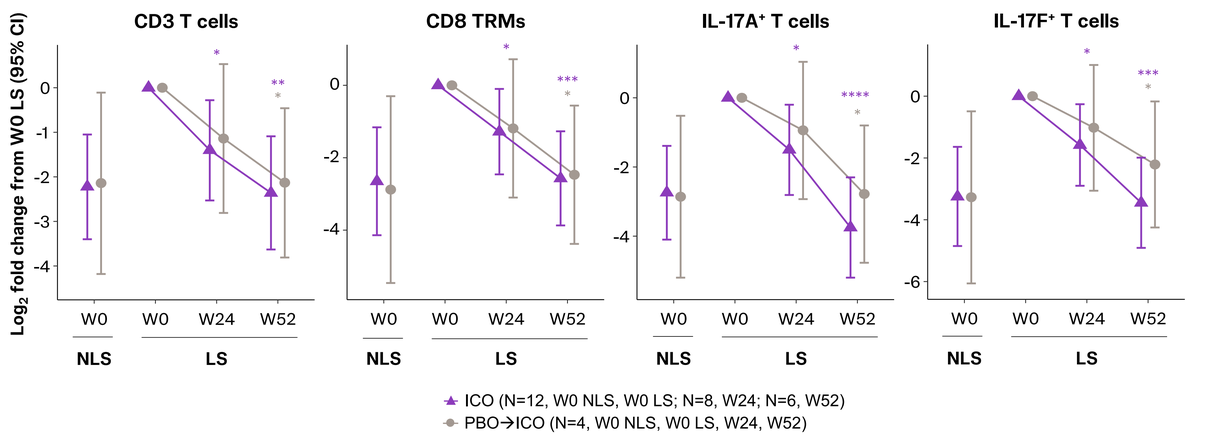




****p<0.001, ****p<0.0001 for LS vs NLS. Data on left-hand side are presented as Tukey boxplots (median, IQR; whiskers = 1.5×IQR).*

ICO significantly reduced T cell counts in LS at W24 and W52 vs W0, with levels approaching NLS at W52

- Reductions in T cell populations observed with ICO by FC analysis were consistent with IF data
- T cell counts were similarly reduced as early as 8 weeks after W16 transition from PBO to ICO



**p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 for change from W0 LS within treatment group. Points show estimated model mean, whiskers show 95% CIs.*

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