

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

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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 role¹

Icotrokinra (ICO)

- First and only IL-23 receptor (IL-23R)-targeted oral peptide that precisely inhibits IL-23 pathway signaling²
- Approved for moderate-to-severe plaque PsO in adults and pediatric patients ≥12 years of age and ≥40 kg³

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 W24⁴
- 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response (Psoriasis Area and Severity Index [PASI] and Investigator's Global Assessment [IGA]) from W24-52 versus those withdrawn to PBO; in adolescents, ICO showed high and durable skin clearance through W52⁵
- ICO adverse event rates were similar to PBO through W16, and did not increase through W52

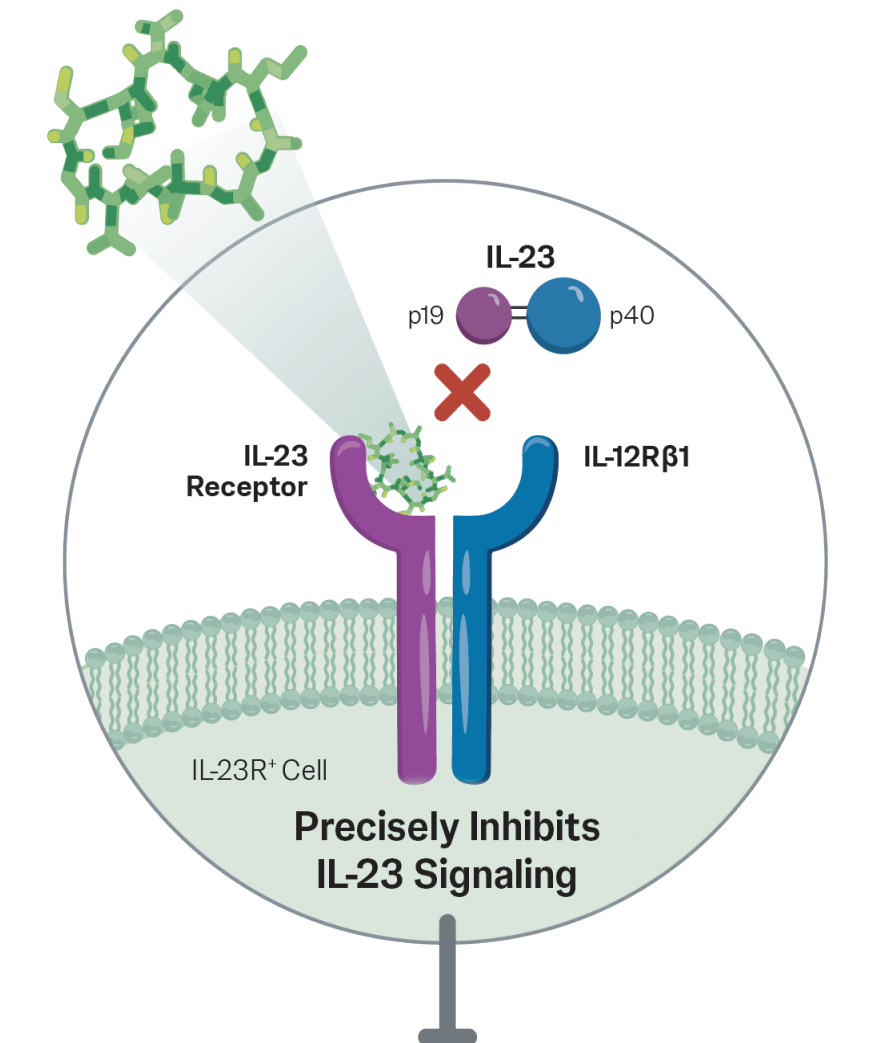
Objective

Evaluate ICO pharmacodynamic 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



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Icotrokinra Blocks IL-23 From Binding to its Receptor

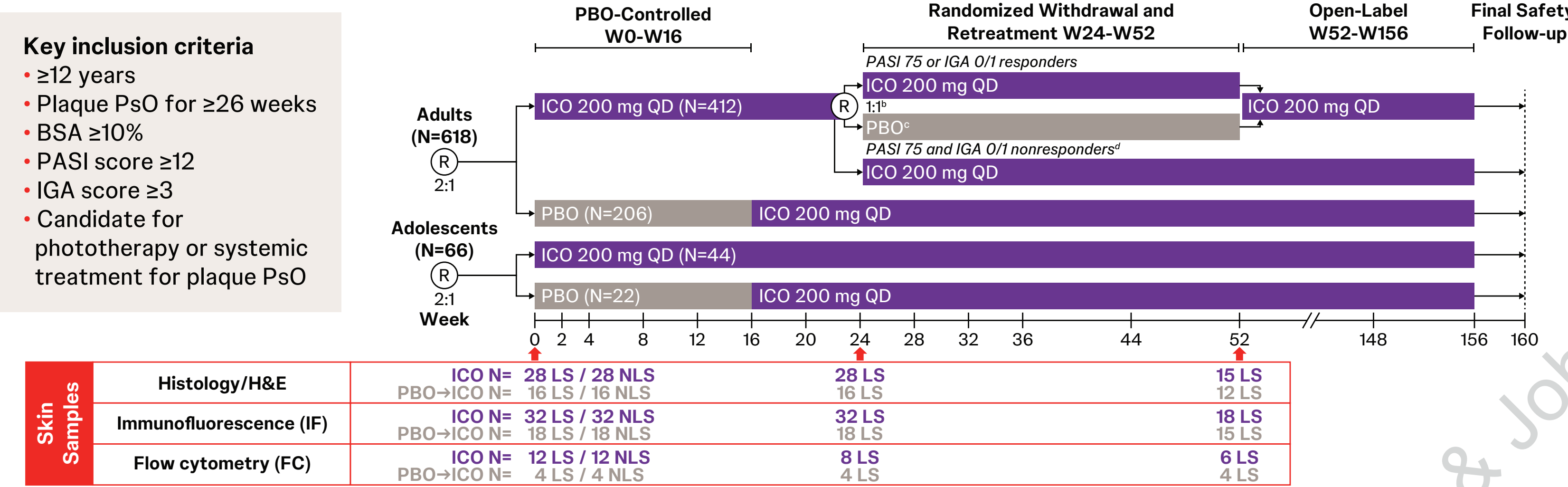


Inhibits IL-17A, IL-17F, IL-22, and IFN-γ Production
IFN=interferon, IL-12Rβ1=interleukin-12 receptor beta 1, IL=interleukin.

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 pharmacodynamic 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

ICONIC-LEAD – Study Design and Skin Sample Analysis^a



^aIn a subset of consenting participants. ^aAt W24, adults who were PASI 75 or IGA score of 0 or 1 responders were rerandomized to continue ICO or PBO. ^aW24 ICO responders rerandomized to PBO at W24 were excluded from W52 biomarker analyses shown here. ^aW24 ICO non-responders and adolescents were included in W52 biomarker analyses shown here. ^aBSA=body surface area, ^aH&E=hematoxylin and eosin, ^aICO=icotrokinra, ^aIGA=Investigator's Global Assessment, ^aLS=lesional skin, ^aNLS=non-lesional skin, ^aPASI=Psoriasis Area and Severity Index, ^aPBO=placebo, ^aPsO=psoriasis, ^aQD=daily, ^aR=randomized, ^aW=week.

Assessments and Analysis

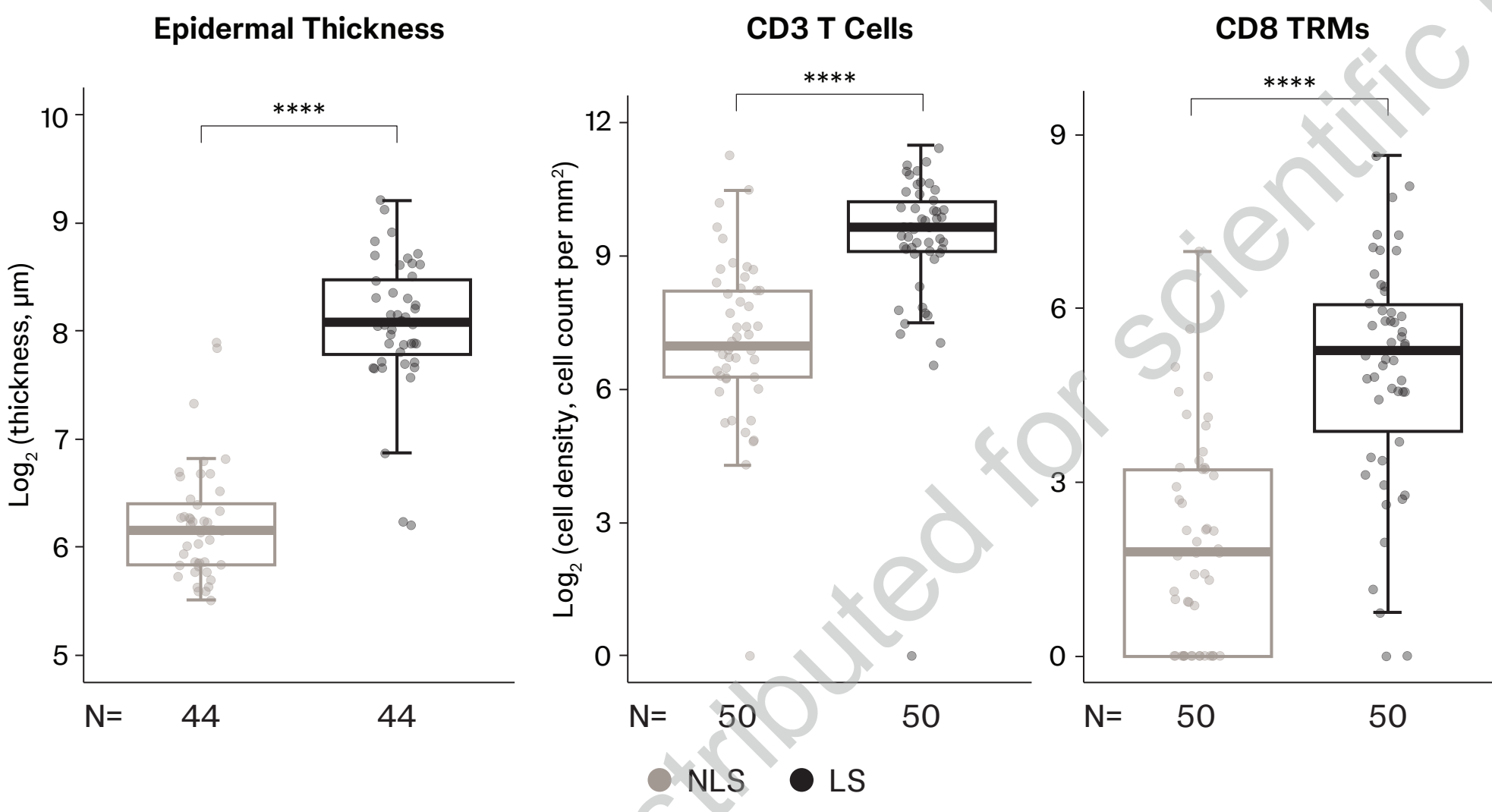
Assessments	Analysis
Skin epidermal thickness Histological analysis using H&E staining^a	- Lesional skin (LS) vs non-lesional skin (NLS) at W0: - One-sample t-tests of log₂ fold change between NLS and LS at W0
T cell densities - Assessed using IF^{a,b,c}: - CD3 T cells - CD8 TRMs (CD3⁺CD8⁺CD103⁺)	- Linear mixed effects modeling of: - W24 and W52 log₂ fold change from W0 LS as associated with treatment group^a - 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: - Log₂ fold change between NLS and LS at W0 with treatment as a fixed effect - Statistical significance was defined as p<0.05

^aAssessed using HALO AI v4.0.5107577 software (Indica Labs). ^bDifferent sets of skin samples were used for IF and FC. ^cImage analysis was performed using HighPlex FL v4.13 algorithm (Indica Labs). ^dSkin 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). ^aAdjusted for W0 levels, interaction between time and treatment, participant random effect, among other covariates. ^aCD=cluster of differentiation, ^aCI=confidence interval, ^aFC=flow cytometry, ^aH&E=hematoxylin and eosin, ^aIF=immunofluorescence, ^aIL=interleukin, ^aTRM=tissue-resident memory T cell, ^aW=week.

Results

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

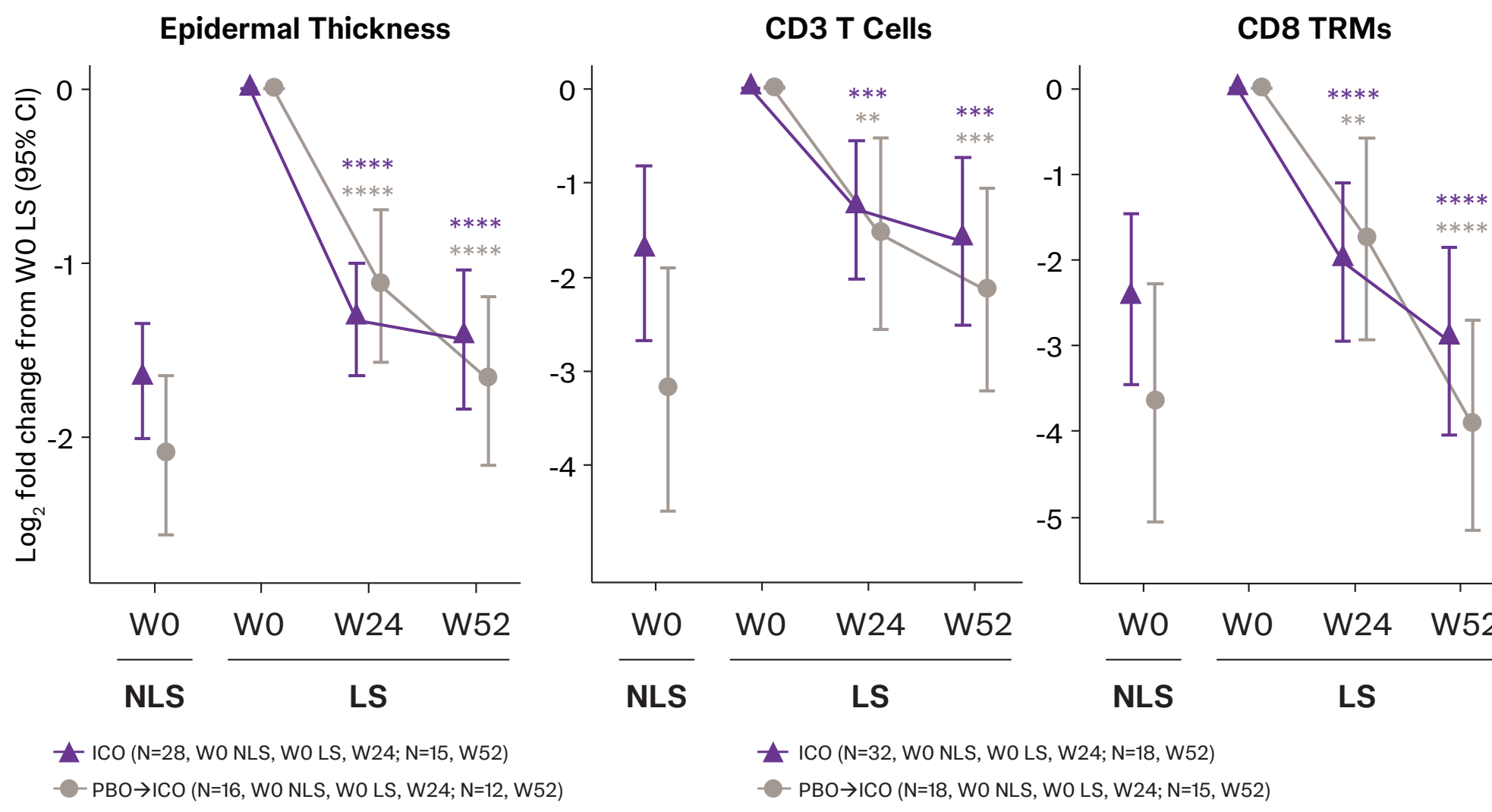
- CD8 TRMs (CD3⁺CD8⁺CD103⁺) that produce IL-17 and are implicated in disease memory, which may contribute to PsO chronicity^{6,7}, are enriched in PsO LS



****p<0.0001 for LS vs NLS. Data are presented as Tukey boxplots (median, interquartile range [IQR]; whiskers = 1.5xIQR). ^aCD=cluster of differentiation, ^aLS=lesional skin, ^aNLS=non-lesional skin, ^aTRM=tissue-resident memory T cell.

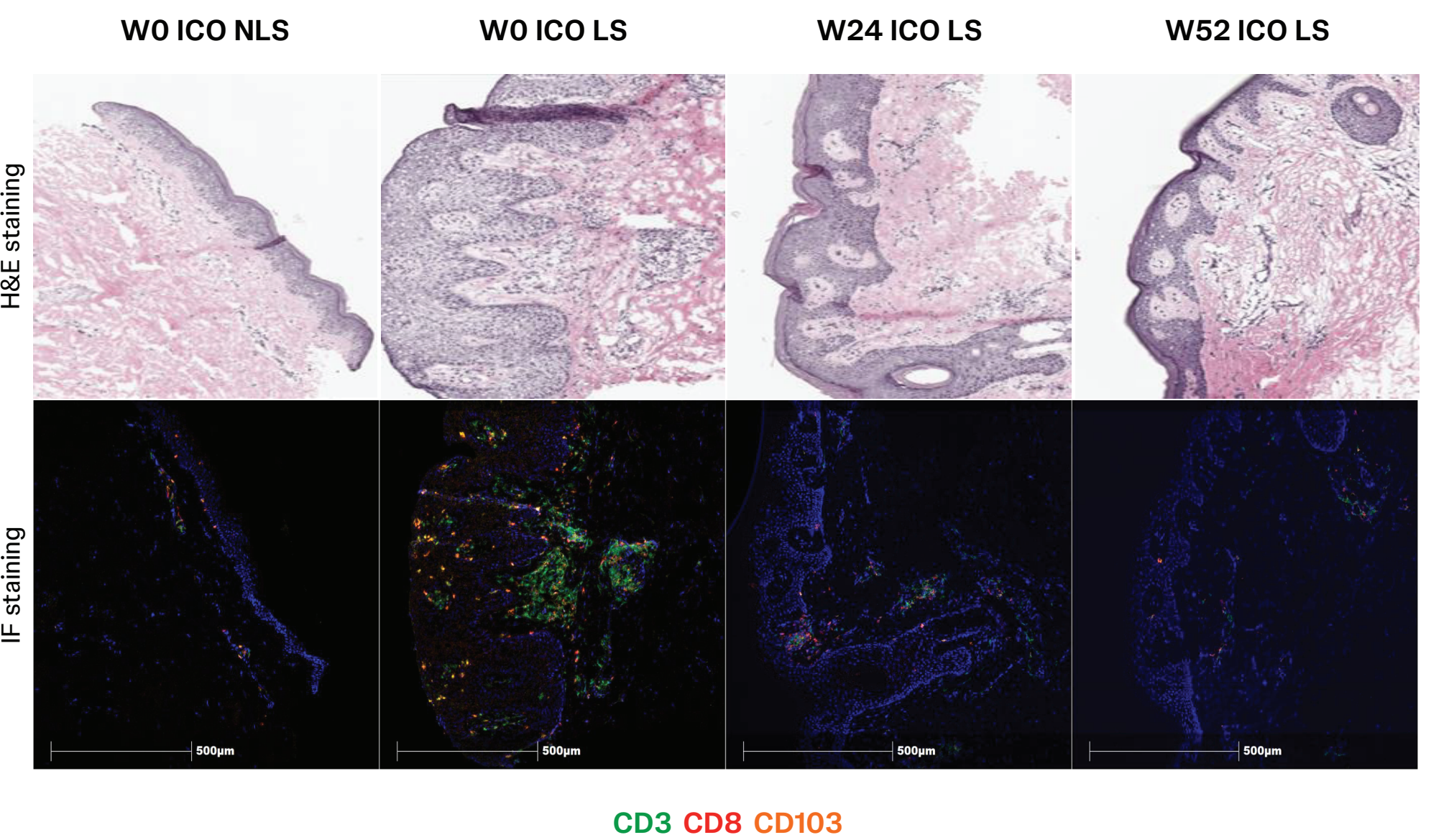
ICO significantly reduced epidermal thickness and T cell densities in LS at W24 and W52 vs W0, with levels approaching NLS at W52

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



****p<0.0001, ****p<0.0001, ****p<0.0001 for change from W0 LS within treatment group. Points show estimated model mean, whiskers show 95% CIs. ^aCD=cluster of differentiation, ^aCI=confidence interval, ^aICO=icotrokinra, ^aLS=lesional skin, ^aNLS=non-lesional skin, ^aPBO=placebo, ^aTRM=tissue-resident memory T cell, ^aW=week.

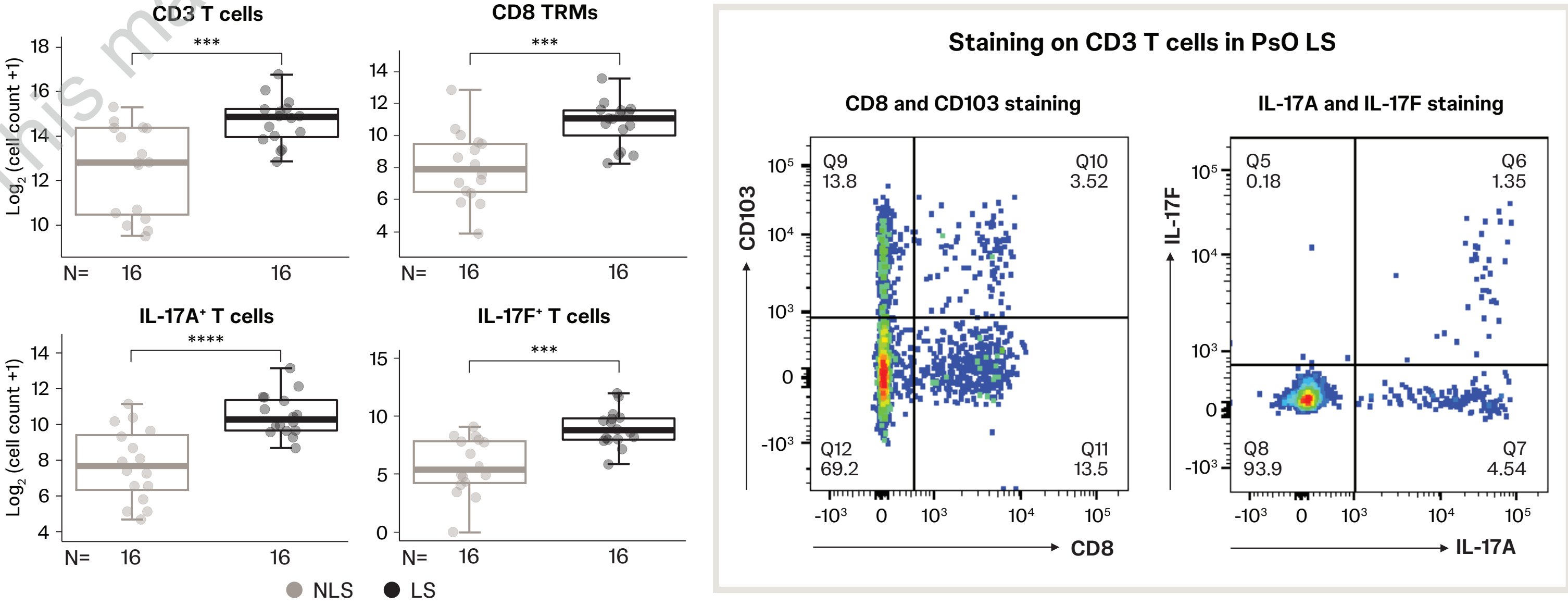
ICO normalized skin architecture and attenuated T cell burden in LS at W24 and W52 vs W0



Images shown are representative of ICO-randomized participants who remained on ICO for 52W (N=15). ^aCD=cluster of differentiation, ^aH&E=hematoxylin and eosin, ^aICO=icotrokinra, ^aIF=immunofluorescence, ^aLS=lesional skin, ^aNLS=non-lesional skin, ^aW=week.

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

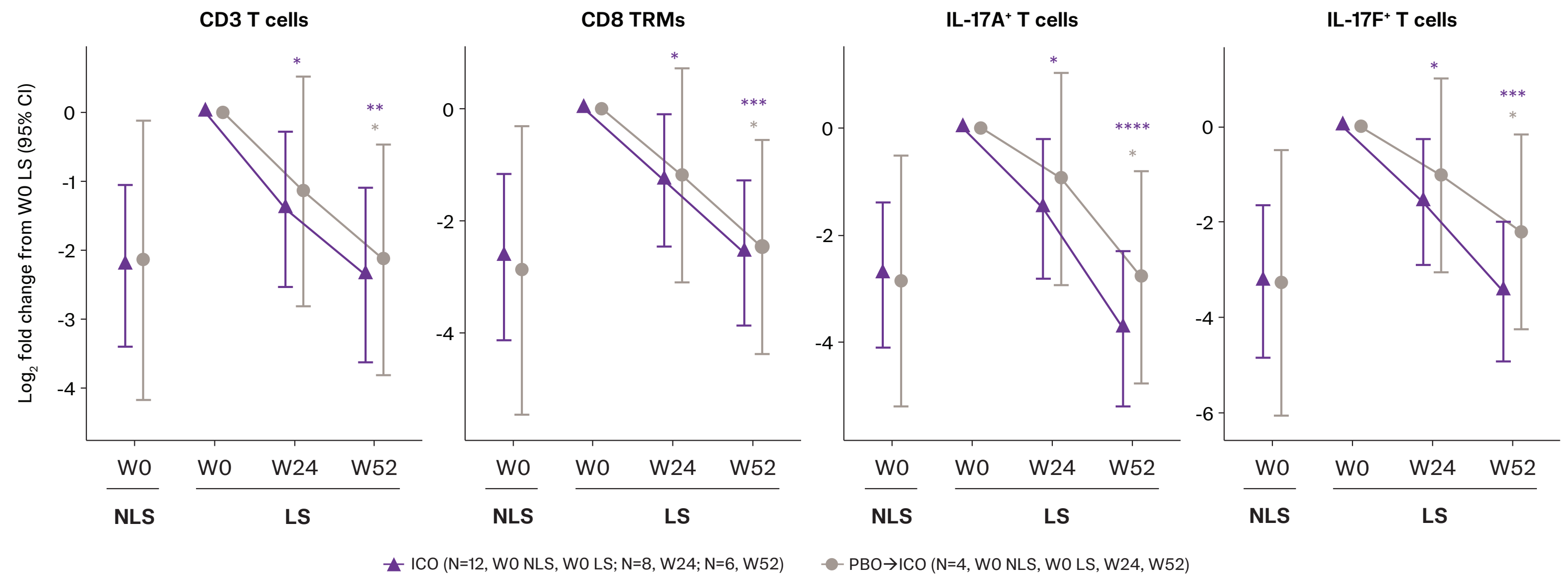
- Consistent with IF data, CD3 T cell staining and FC analysis showed expansion of T cell populations in LS at W0



****p<0.0001, ****p<0.0001 for LS vs NLS. Data on left-hand side are presented as Tukey boxplots (median, IQR; whiskers = 1.5xIQR). ^aCD=cluster of differentiation, ^aIL=interleukin, ^aIQR=interquartile range, ^aLS=lesional skin, ^aNLS=non-lesional skin, ^aPsO=psoriasis, ^aTRM=tissue-resident memory T cell.

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. ^aCD=cluster of differentiation, ^aCI=confidence interval, ^aICO=icotrokinra, ^aIL=interleukin, ^aLS=lesional skin, ^aNLS=non-lesional skin, ^aPBO=placebo, ^aTRM=tissue-resident memory T cell, ^aW=week.