

Durability of Systemic and Skin Pharmacodynamic Responses With Icotrokinra in Moderate-to-Severe Plaque Psoriasis: Phase 3 ICONIC-LEAD Week 52 Results

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Background

Plaque psoriasis (PsO) is an immune-mediated chronic inflammatory skin disease driven by dysregulation of the interleukin (IL)-23 pathway¹

Icotrokinra (ICO) is the first and only targeted oral peptide that precisely blocks the IL-23 receptor (IL-23R) and inhibits IL-23 pathway signaling²

- Approved for moderate-to-severe plaque PsO in adults and adolescents (≥12 years of age and ≥40 kg)³

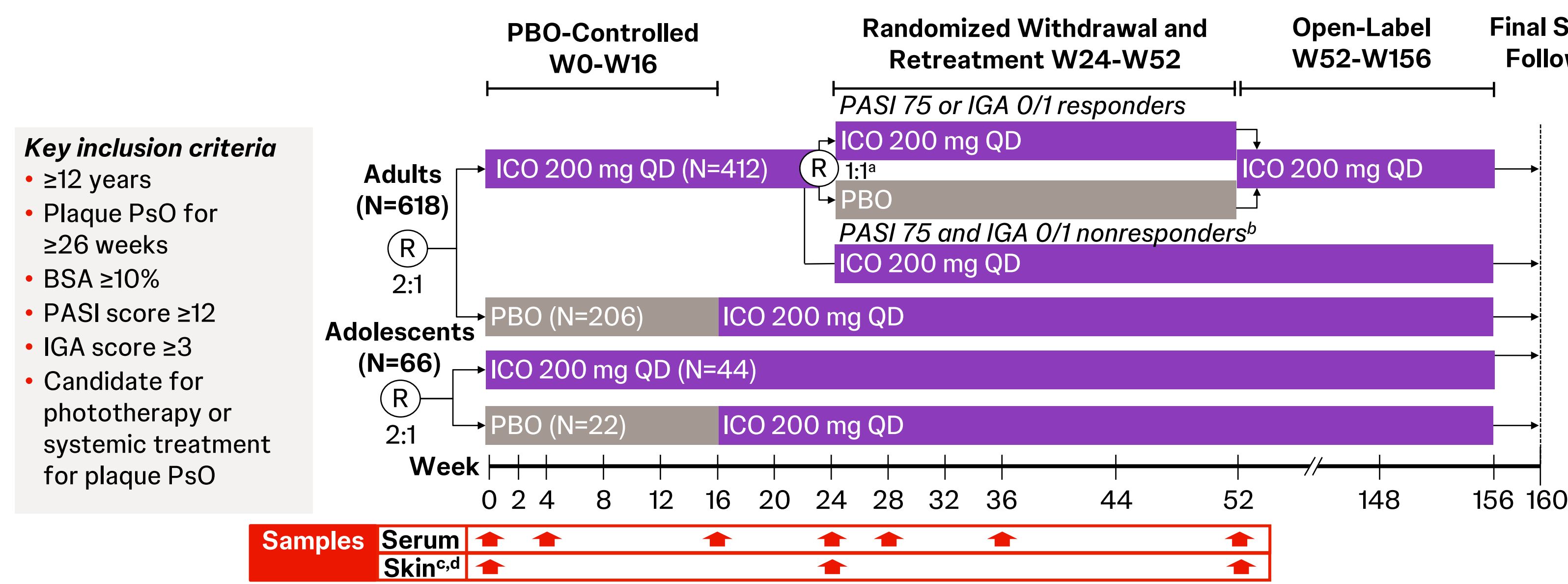
ICONIC-LEAD (NCT06095115)

- Ongoing phase 3 randomized, double-blind, placebo (PBO)-controlled study assessing the efficacy and safety of once-daily ICO in adults and adolescents with moderate-to-severe plaque PsO^{4,5,6}
- At Week (W)16, ICO demonstrated significantly higher skin clearance vs PBO, with responses increasing through W24⁴
- From W24-W52, continuing ICO in adults demonstrated superior maintenance of skin response (Psoriasis Area and Severity Index [PASI] and Investigator's Global Assessment [IGA]) versus those withdrawn to PBO⁵
 - ICO showed high and durable skin clearance rates through W52 in adolescents⁶
- Adverse events through W16 and up to W52 were similar with PBO and ICO

Objective

Evaluate ICO pharmacodynamic (PD) effects on serum protein and skin gene expression through W52 among adult and adolescent participants with moderate-to-severe plaque PsO in ICONIC-LEAD

ICONIC-LEAD – Study Design and Sample Collection

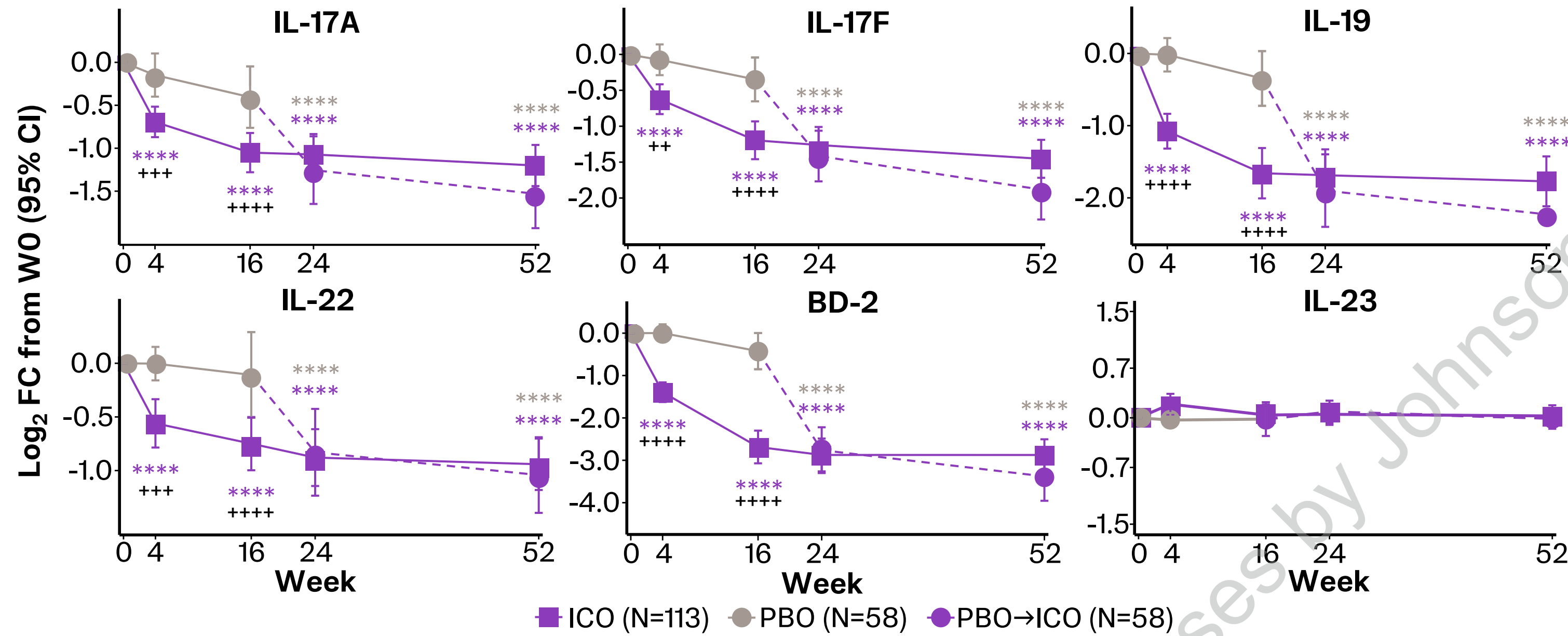


^aAt W24, adults who were PASI 75 or IGA score of 0 or 1 responders were randomized to continue ICO or PBO. ^bW24 ICO non-responders and adolescents were included in W52 biomarker analyses shown here. ^cSkin biopsies were collected from consenting participants of an optional sub-study. ^dLesional (LS) and non-lesional (NLS) skin samples were collected at W0, only LS samples were collected at the remaining timepoints. ^eAdjusted for W0 levels, interaction between time and treatment, participant random effect, among other covariates. ^fBD-2=beta defensin-2, ^gBSA=body surface area, ^hELISA=enzyme-linked immunosorbent assay, ⁱGSEA=gene set enrichment analysis, ^jMSD=Merck Sharp & Dohme, ^kQD=daily, ^lR=randomized, ^mR&D=research and development, ⁿRNA-seq=RNA sequencing, ^oSMC=single molecule counting.

Results

ICO significantly reduced serum IL-17A, IL-17F, IL-19, IL-22 and BD-2 as early as W4 and through W52

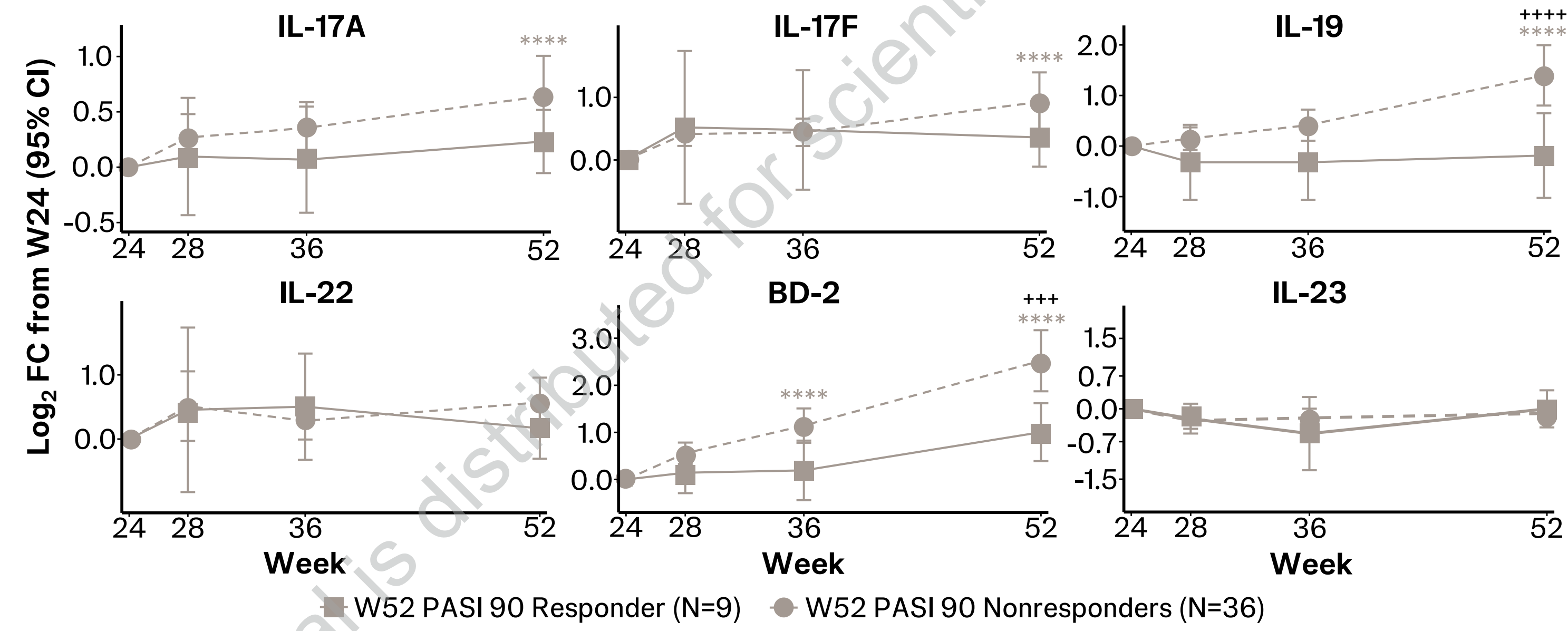
- Serum IL-17A, IL-17F, IL-19, BD-2 levels significantly reduced as early as 8 weeks after transition from PBO to ICO
- Serum IL-23 levels were stable through W52 of ICO



***p<0.0001 change from W0 within treatment group / +p<0.01, +++p<0.001, ++++p<0.0001 for ICO vs PBO. W24 ICO responders randomized to PBO at W24 were excluded from W0-W52 biomarker analyses. Points show estimated model mean, whiskers show 95% CIs. CI=confidence interval.

Adult W24 ICO responders re-randomized to PBO who maintained a PASI 90 response at W52 maintained reduced serum IL-17A, IL-17F, IL-19, and BD-2 levels through W52

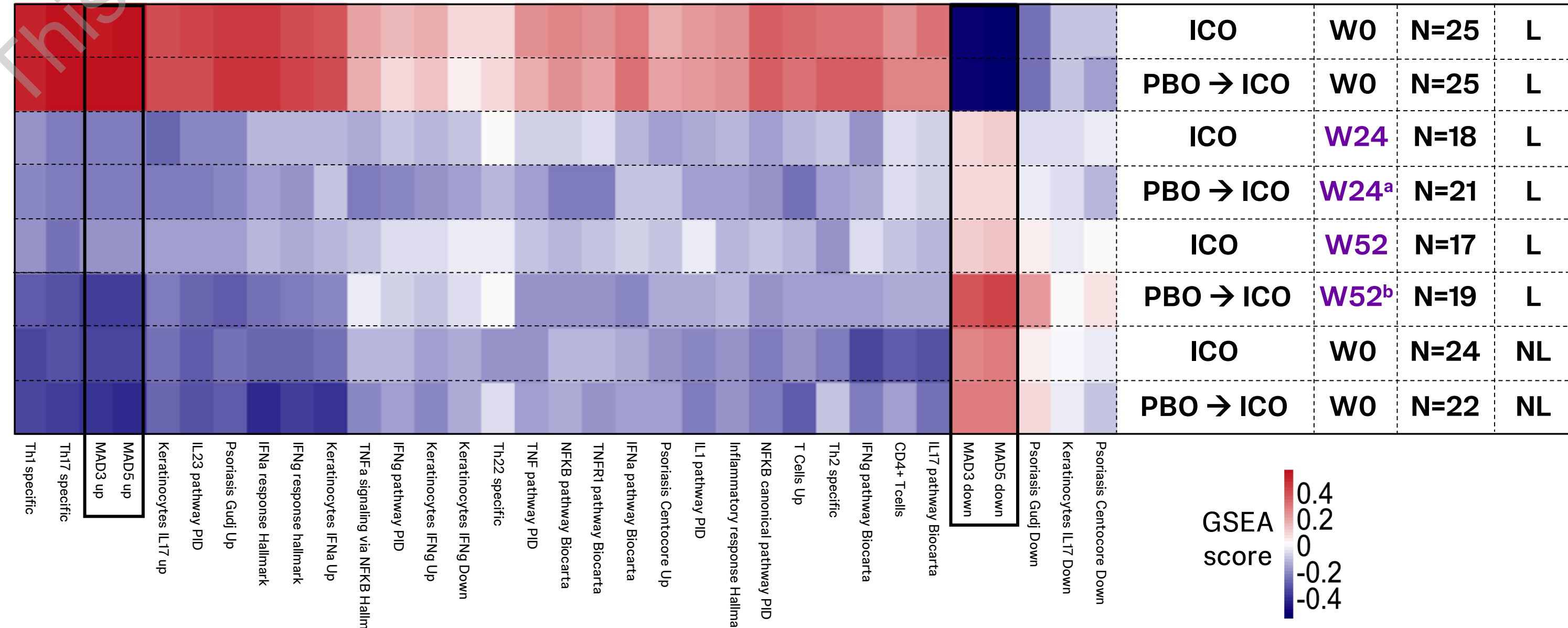
- Adult W24 ICO responders^a re-randomized to PBO who did not achieve W52 PASI 90 response showed gradual increases in serum IL-17A, IL-17F, IL-19 and BD-2 levels
- IL-22 and IL-23 serum levels remained stable regardless of W52 PASI 90 response status



***p<0.0001 change from W24 within W52 PASI 90 response group^b / +++p<0.001, ++++p<0.0001 for W52 PASI 90 Responders vs W52 PASI 90 Nonresponders. Points show estimated model mean, whiskers show 95% CIs. ^aPASI 75 or IGA score of 0 or 1 responders at W24. ^bNo significant change from W24 were observed in the W52 PASI 90 Responders group.

ICO reduced PsO-related gene set enrichment scores in LS at W24 and W52 vs W0, with scores approaching NLS as early as W24

- ICO-induced changes in PsO-related gene set enrichment scores as early as 8 weeks after W16 transition from PBO to ICO



^a8 weeks on ICO treatment. ^b36 weeks on ICO treatment.

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Key Takeaways

✓ In the phase 3 ICONIC-LEAD in adults and adolescents with plaque PsO, ICO robustly and durably reduced serum and skin biomarkers of IL-23 pathway activation

- ✓ ICO significantly reduced serum IL-17A, IL-17F, IL-19, IL-22, and BD-2 levels as early as W4 and through W52
- ✓ In adult W24 ICO responders, continuous ICO sustained systemic PD effects through W52; effects were also durable after withdrawal in those maintaining PASI 90 response at W52
- ✓ ICO reduced lesional skin PsO-related gene expression toward non-lesional skin levels at W52; reductions were observed as early as 8 weeks after the transition from PBO-to-ICO
- ✓ ICO PD effects on disease-related skin gene expression were sustained through W52 with continuous ICO and after withdrawal without retreatment

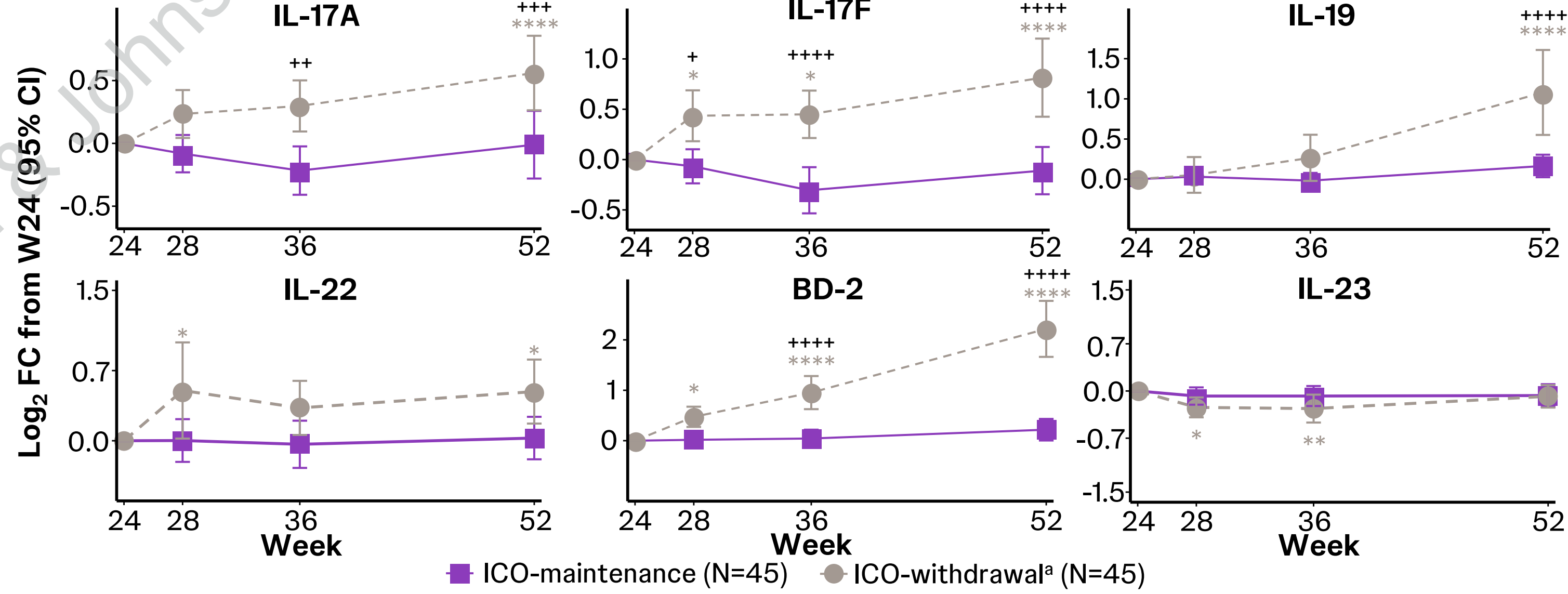
✓ These comprehensive biomarker findings are consistent with the significant skin clearance achieved with this first and only IL-23R-targeted oral peptide that precisely inhibits the IL-23 pathway

Assessments and Analysis

Assessments	Analysis
Systemic PD - Assessed using S-PLEX assay by MSD: - IL-17A - Assessed using SMC assay by Millipore: - IL-17F, IL-23, IL-22 (custom) - Assessed using ELISA by R&D system: - IL-19 - Assessed using custom assay by MSD: - BD-2	- Linear mixed-effects modeling of: - Log₂ fold change (FC) from W0 within treatment group - Log₂ FC from W24 for ICO-maintenance vs ICO-withdrawal^a during the randomized-withdrawal period - Log₂ FC from W24 for PBO-re-randomized W52 PASI 90 responders vs nonresponders during the randomized-withdrawal period^a - Statistical significance was defined as p≤0.05
Skin PD Assessed using RNA-seq	- Linear mixed-effects modeling of: - Log₂ normalized gene expression counts at W24 and W52 vs W0 within treatment group - Log₂ normalized gene expression counts at W52 vs W24 within treatment group - GSEA scores evaluated across immune and PsO-related gene set pathways in NLS at W0 and LS at W0, W24, and W52 - Statistical significance was defined as p≤0.05

Adult W24 ICO responders re-randomized to continuous ICO sustained reduced serum biomarker levels through W52

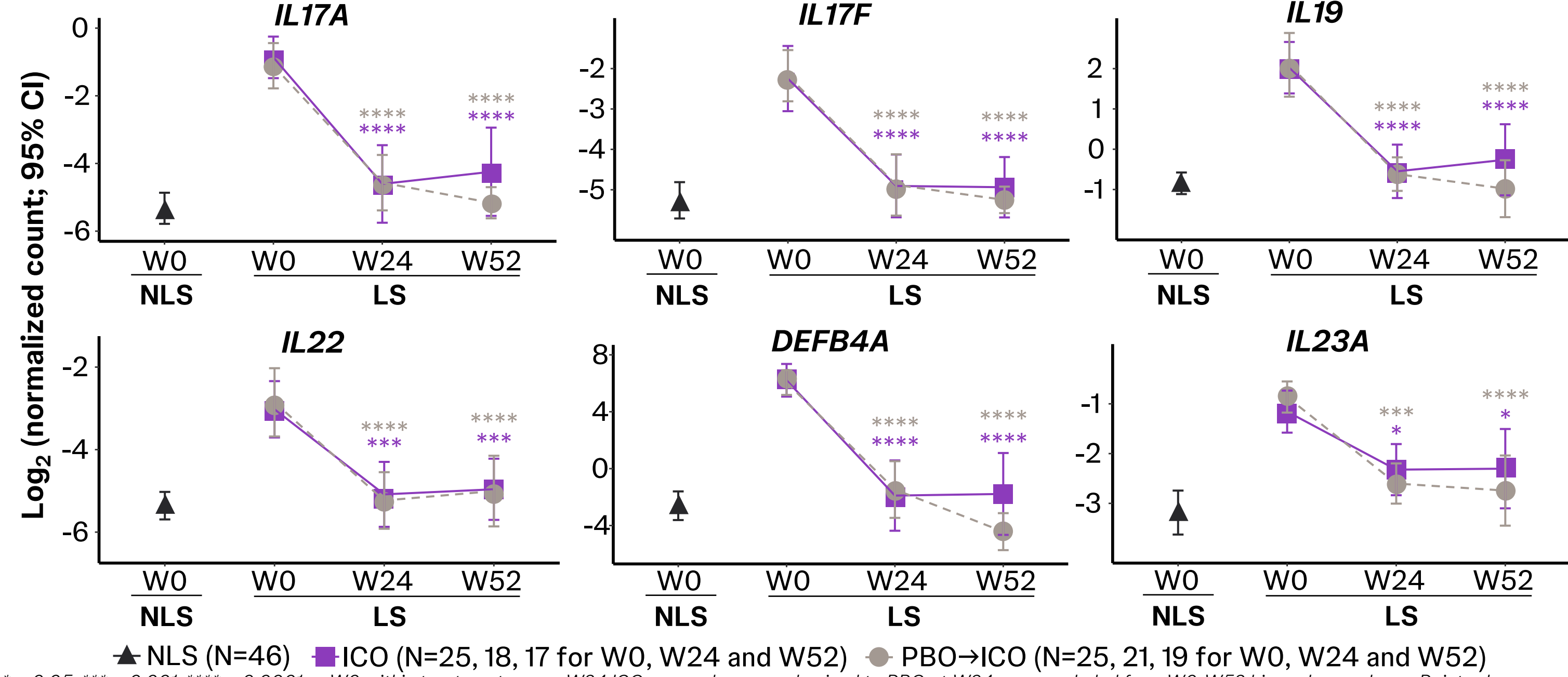
- Adult W24 ICO responders re-randomized to PBO (withdrawal) showed gradual increases in serum IL-17A, IL-17F, IL-19 and BD-2 levels through W52
- Comparatively, no difference in IL-22 or IL-23 levels was observed for ICO-maintenance vs ICO-withdrawal groups



*p<0.05, **p<0.01, ***p<0.0001 change from W24 within treatment group^a / *p<0.05, **p<0.01, ***p<0.001 for ICO-maintenance vs ICO-withdrawal. Points show estimated model mean, whiskers show 95% CIs. ^aParticipants withdrew from ICO at W24 and remained on PBO through W52. ^bNo significant change from W24 were observed in the ICO-maintenance group.

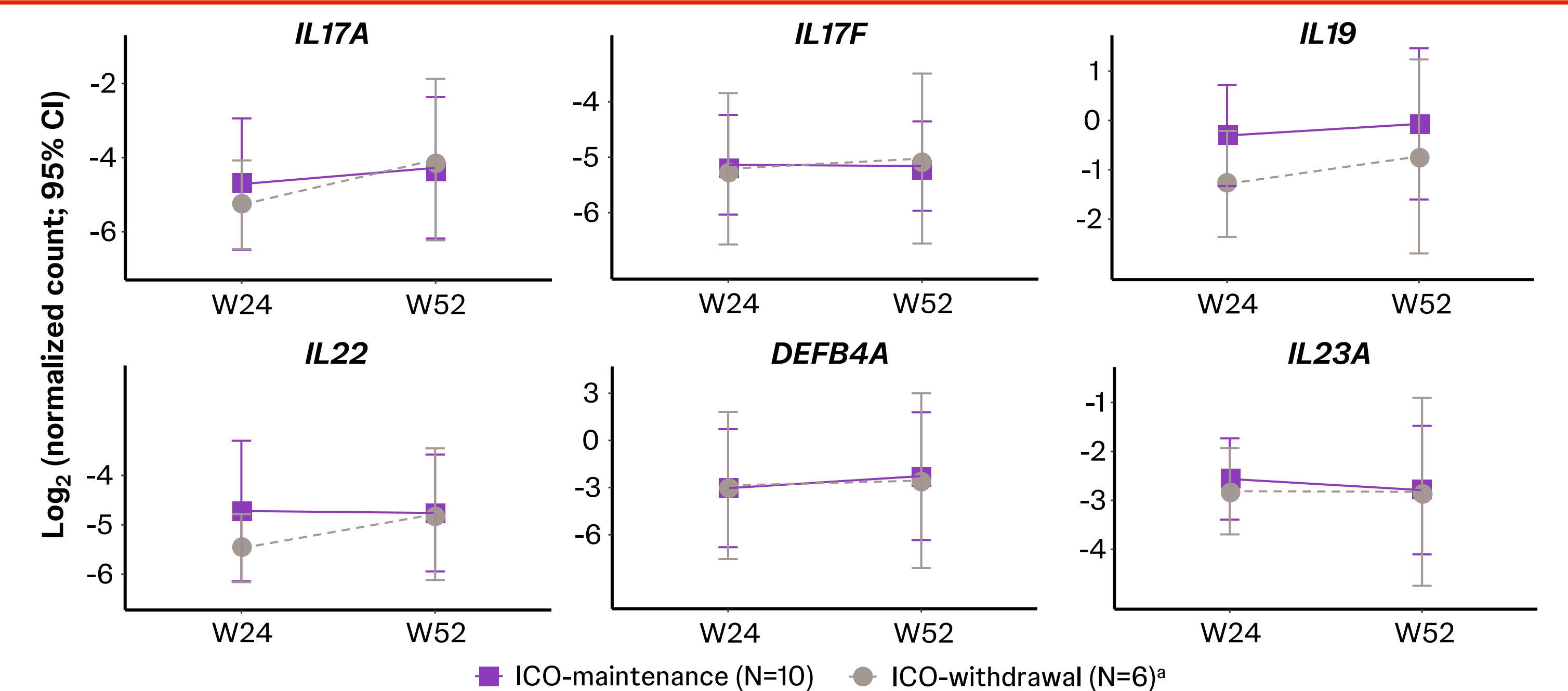
ICO significantly reduced the expression of key inflammatory genes in LS at W24 and W52 vs W0, with levels approaching NLS

- Expression of key inflammatory genes was significantly reduced as early as 8 weeks after W16 transition from PBO to ICO



*p<0.05, ***p<0.001, ****p<0.0001 vs W0 within treatment group. W24 ICO responders rerandomized to PBO at W24 were excluded from W0-W52 biomarker analyses. Points show estimated model mean, whiskers show 95% CIs.

Adult W24 ICO responders sustained reduced inflammatory gene expression in LS through W52 in both ICO-maintenance and ICO-withdrawal (no retreatment) arms



Points show estimated model mean, whiskers show 95% CIs. ^aParticipants withdrew from ICO at W24 and remained on PBO through W52.