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 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

All W24 adults who were PASI 75 or IGA score of 0 or 1 response were randomized to continue CO or **PB0**. W24 CO non-responders and adolescents were included in W52 biomarker analyses shown here. Skin biopsies were collected from consenting participants of an optional sub-study. Lesional (LS) and non-lesional (NLS) skin samples were collected at W0, only LS samples were collected at the remaining timepoints. *Adjusted for W0 levels. Interaction between time and treatment protocol random effect among covariates. **BSA**=body surface area, **ICQ**=ictotikroin, **IFN**=interferon, **IGA**=Investigator's Global Assessment, **I**=interleukin, **NLS**=non-lesional skin, **PASI**=Psoriasis Area and Severity Index, **PB0**=placebo, **PD**=pharmacodynamic, **PSO**=psoriasis, **OD**=once daily, **R**=randomized, **RNA**=RNA sequencing, **S-PLEX**=Single Molecule Counting Protein Assay, **W**=week

*p<0.05, **p<0.01, ***p<0.0001 change from W24 within treatment group/ †p<0.05, ††p<0.01, †††p<0.001 ††††p<0.0001 for ICO-maintenance vs ICO-withdrawal. Points show estimated model mean, whiskers show 95% CI. †Participants withdrew from ICO at W24 and remained on PBO through W52. ††No significant change from W24 were observed in the ICO-maintenance group. **BD-2**=beta defensin 2. **CI**=confidence interval. **FC**=fold change, **ICO**=icotrokinra, **I**=interleukin, **N**=number of participants, **PBO**=placebo, **W**=week

*8 weeks on ICO treatment, *36 weeks on ICO. **BD-2**=beta defensin-2, **CD4+**=cluster of differentiation 4 positive, **ELISA**=enzyme-linked immunosorbent assay, **GSEA**=gene set enrichment analysis, **ICO**=icotritin, **IFN**=interferon, **IL**=interleukin, **LS**=lesional, **MAD**=mean absolute deviation, **N**=number of participants, **NFKB**=nuclear factor kappa B, **NF**=non-lesional, **NLS**=non-lesional skin, **PBO**=placebo, **PID**=pathway interaction database, **PsO**=psoriasis, **SMC**=single molecule counting, **Th-T**=helper, **TNF**=tumor necrosis factor, **TNFR1**=tumor necrosis factor receptor 1, **W**=week

Figure 2 displays six line graphs showing the Log₂ fold change of gene expression in the brain for various cytokines and chemokines at two time points (W24 and W52) for two groups: ICO-maintenance (N=10) and ICO-withdrawal (N=6). The y-axis represents Log₂ (normalized count; 95% CI). The x-axis shows W24 and W52. The legend indicates that purple squares represent ICO-maintenance (N=10) and grey circles represent ICO-withdrawal (N=6).

The genes shown are IL17A, IL17F, IL19, IL22, DEFB4A, and IL23A. In all cases, the ICO-withdrawal group shows a decrease in expression from W24 to W52 compared to the ICO-maintenance group.

Gene	Group	W24 Log ₂ (95% CI)	W52 Log ₂ (95% CI)
IL17A	ICO-maintenance (N=10)	-4.5	-4.2
	ICO-withdrawal (N=6)	-5.5	-4.5
IL17F	ICO-maintenance (N=10)	-5.2	-5.2
	ICO-withdrawal (N=6)	-5.5	-5.5
IL19	ICO-maintenance (N=10)	-0.5	-0.2
	ICO-withdrawal (N=6)	-1.2	-0.8
IL22	ICO-maintenance (N=10)	-4.8	-4.8
	ICO-withdrawal (N=6)	-5.5	-4.8
DEFB4A	ICO-maintenance (N=10)	-2.8	-2.5
	ICO-withdrawal (N=6)	-3.0	-2.8
IL23A	ICO-maintenance (N=10)	-2.8	-2.8
	ICO-withdrawal (N=6)	-2.8	-2.8

 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