Early Systemic and Skin Pharmacodynamic Effects of Icotrokinra in Participants with Moderate-to-Severe Plaque Psoriasis: Results Through Week 24 of the Phase 3, ICONIC-LEAD Study

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P2808

Key Takeaways

- **ICO demonstrated both *early* and *substantial* PD effects, with levels of IL-23 pathway biomarkers for systemic and skin inflammation normalizing to a healthy state**
- **Serum protein data demonstrated:**
  - ✓ **Reduction of PsO serum biomarkers as early as W4 with continued reduction through W16**
  - ✓ **Serum levels approaching those of healthy controls**
- **Skin transcriptomic data showed:**
  - ✓ **Reduction of PsO skin biomarkers as early as 8 weeks after starting ICO following crossover**
  - ✓ **Normalization of skin inflammation towards baseline non-lesional skin at W24**
  - ✓ **Similar outcomes were achieved with ICO treatment or following crossover to ICO**
- **These comprehensive biomarker findings are consistent with significant skin clearance achieved with this first in class targeted oral peptide to selectively inhibit IL-23 pathway activation**

Background

Icotrokinra (ICO) is a first-in-class, targeted oral peptide for plaque psoriasis (PsO) that selectively binds the interleukin (IL)-23 receptor and **inhibits IL-23 pathway signaling**[1]

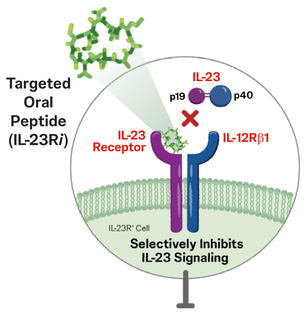
ICONIC-LEAD, a Phase 3 study of ICO in adults and adolescents with moderate-to-severe plaque PsO demonstrated efficacy and safety[2]

- Co-primary endpoints were met with once daily ICO showing significant skin clearance vs placebo (PBO) at Week (W) 16
  - IGA 0/1: 65% (ICO) vs 8% (PBO)
  - PASI90: 50% (ICO) vs 4% (PBO)
- ICO demonstrated separation from PBO as early as W4, with increasing response rates through W24
- Similar adverse event rates between ICO and PBO through W16, and no safety signals emerged through W24

Objectives

To evaluate ICO pharmacodynamic (PD) effects using serum and tissue biomarker data from the pivotal ICONIC-LEAD study through W24

ICO mechanism of action



Inhibits IL-17A, IL-17F and IL-22 production by activated T cells

Inhibits keratinocyte activation/hyperproliferation and production of IL-19 and beta defensin-2 (BD-2)

Restoration of immune homeostasis

BD-2=beta defensin-2, ICO=icotrokinra, IFN=interferon, IGA=Investigator's Global Assessment, IL=interleukin, IL-12Rβ1=interleukin-12 receptor beta 1, IL-23R=interleukin-23 receptor, IL-23Ri=interleukin-23 receptor inhibitor, PASI=Psoriasis Area and Severity Index, PBO=placebo, PsO=psoriasis, W=week.

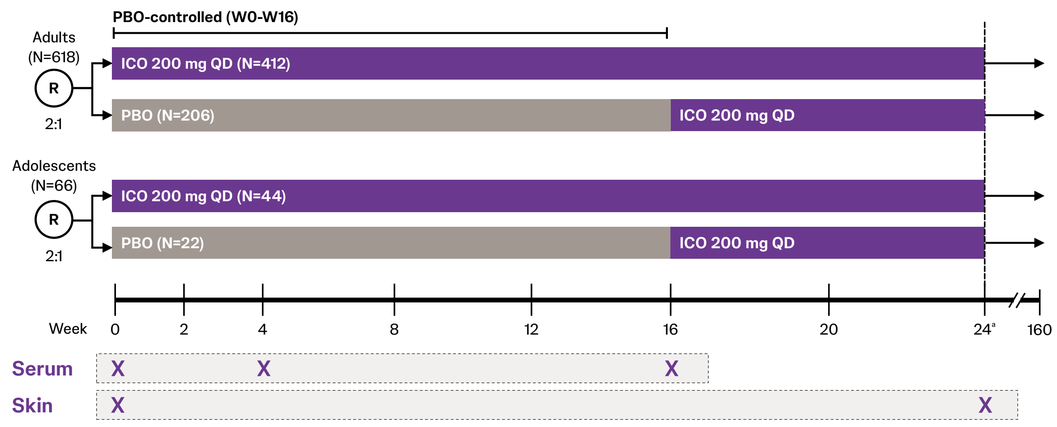
Methods

ICONIC-LEAD Study Design and Biomarker Sample Collection Up to W24

Moderate-to-severe plaque PsO (N=684)

Key inclusion criteria

- ≥12 years
- Plaque PsO for ≥26 weeks
- Body surface area (BSA) ≥10%, Psoriasis Area and Severity Index (PASI) score ≥12, and Investigator's Global Assessment (IGA) score ≥3
- Candidate for phototherapy or systemic treatment for plaque PsO



[a]*At W24, adult participants who are PASI 75 or IGA score of 0 or 1 responders will be re-randomized to continue ICO or PBO*

BSA=body surface area, ICO=icotrokinra, IGA=Investigator's Global Assessment, PASI=Psoriasis Area and Severity Index, PBO=placebo, PsO=psoriasis, QD=daily, R=randomization, W=week.

ICONIC-LEAD Biomarker Data Generation and Analysis

Systemic PD:

- Serum samples were analyzed for PsO-relevant biomarkers: IL-17A, IL-17F, IL-19, IL-22, and beta defensin-2 (BD-2)
- W0, W4, and W16 serum samples from a sub-cohort of 166 (IL-22) and 167 (IL-17A, IL-17F, IL-19, and BD-2) study participants were analyzed. 53 subjects were on PBO, 113 (IL-22) and 114 (other cytokines) on ICO
- Serum samples from a distinct healthy cohort of 30 subjects was included as control (BioIVT, Hicksville, NY)
- Serum IL-17A was measured with an S-PLEX assay by MSD, IL-17F was measured using SMC assay by Millipore, IL-19 was measured with an ELISA assay by R&D Systems, IL-22 was measured using custom SMC assay by Millipore, and BD-2 was measured using custom assay by MSD

Tissue PD:

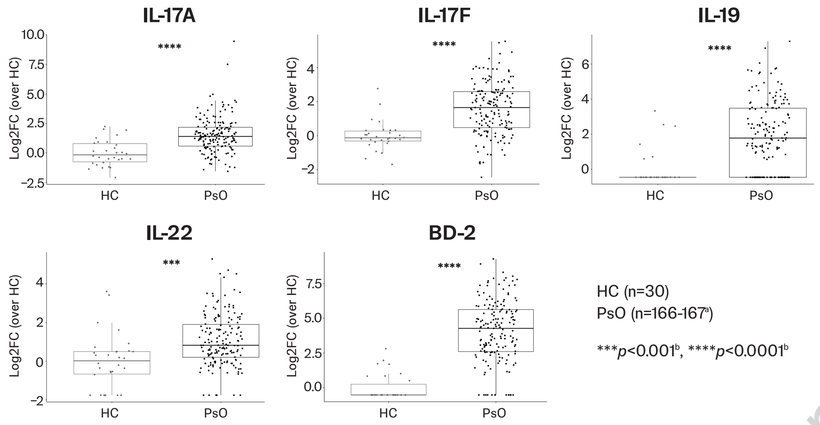
- Skin biopsies samples were used for transcriptomic analysis using RNA sequencing
- W0 non-lesional and lesional and W24 (8 weeks after PBO crossover) lesional skin samples from 46-65 consenting participants of an optional sub-study were analyzed

Data Analysis:

- Comparison between ICO and PBO used linear mixed-effect modeling that included effects for W0 levels, interaction between time and treatment, participant random effect, and other co-variates as appropriate
- Statistical significance was defined as having *p*-value ≤0.05; for volcano plot, adjusted *p*-value ≤0.05 and |logFC|>1

Results

At baseline, IL-17A, IL-17F, IL-19, IL-22, and BD-2 serum levels are elevated in PsO compared to healthy controls (HC)



HC (n=30)
PsO (n=166-167[a])

***p<0.001[b], ****p<0.0001[b]

[a]n=166 for IL-22, n=167 for all other cytokines; [b]p-values based on two-sided Welch T test. Figures plotted as median and interquartile range. Each point denote individual log2FC over mean of log2concentration of HC samples. BD-2=beta defensin-2, FC=fold change, HC=healthy controls, IL=interleukin.

ICO improved skin PD as early as W8 and normalized PsO lesional skin transcriptome towards baseline non-lesional skin by W24

Baseline lesional skin is highly differentiated from non-lesional skin

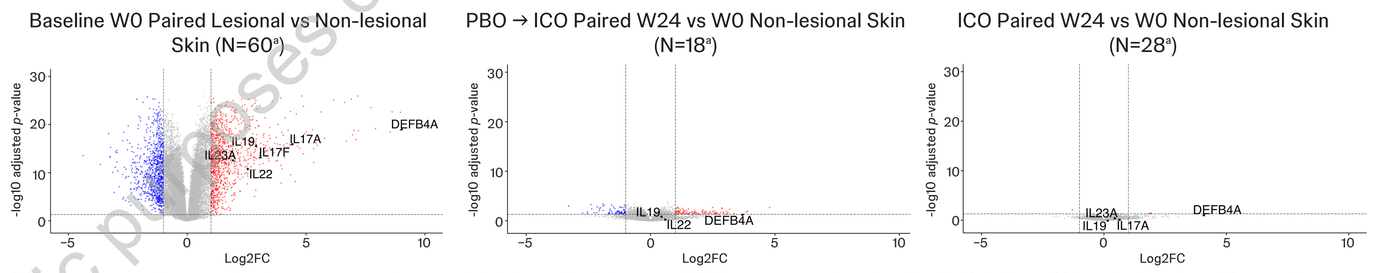
Baseline W0 Paired Lesional vs Non-lesional Skin (N=60[a])

ICO elicited early impact on skin transcriptome (8 weeks of ICO treatment)

PBO → ICO Paired W24 vs W0 Non-lesional Skin (N=18[a])

ICO normalized overall skin transcriptome toward baseline non-lesional state at W24

ICO Paired W24 vs W0 Non-lesional Skin (N=28[a])

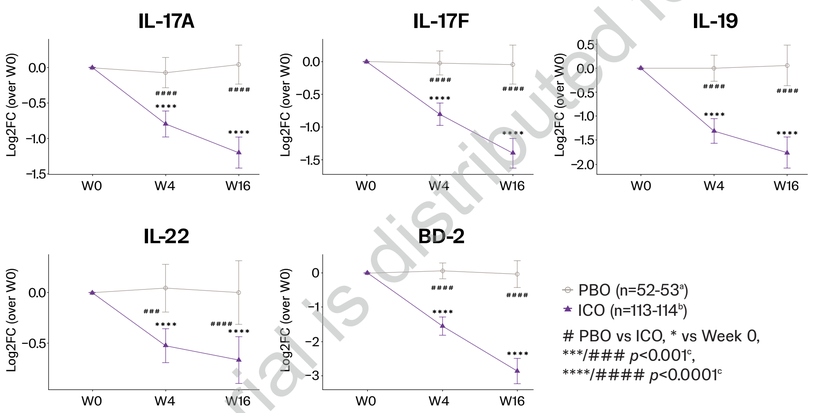


- Downregulated in lesional skin (log2FC≤1, adjusted *p*-value <0.05)
- Upregulated in lesional skin (log2FC>1, adjusted *p*-value <0.05)

[a]*Subject number reported with each plot is based on the actual number of samples available for that specific paired time points. DEFB4A=gene that encodes human beta-defensin 2, FC=fold change, ICO=icotrokinra, IL=interleukin, PBO=placebo, PD=pharmacodynamics, W=week.*

- At W0, 1020 genes were significantly upregulated and 917 significantly downregulated in lesional vs non-lesional skin (paired sample analysis). *In a similar unpaired sample analysis, (n=65) 1026 genes were significantly upregulated and 970 significantly downregulated.*
- In PBO → ICO cohort, majority of genes have been normalized to baseline non-lesional skin level 8 weeks after crossover from PBO to ICO.
- In ICO cohort, overall normalization of skin transcriptome toward baseline non-lesional skin was seen after 24 weeks of treatment.

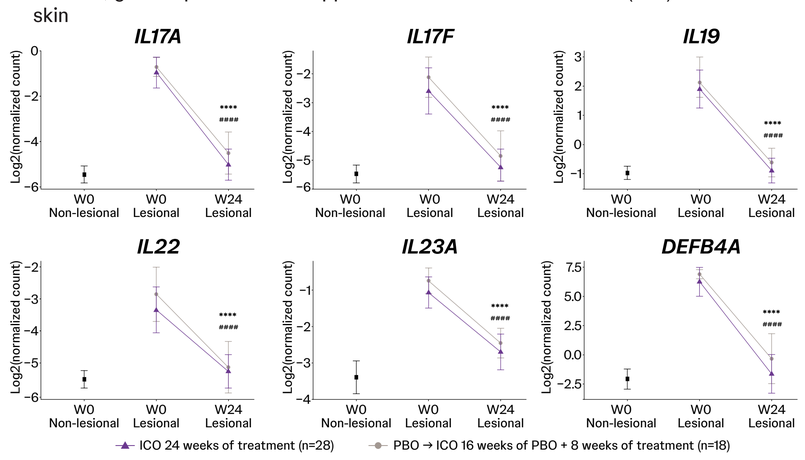
ICO reduced serum levels of PsO relevant biomarkers as early as W4 with continued reduction through W16



[a]n=52-53 for IL-22, n=53 for all other cytokines; [b]n=113 for IL-22, n=114 for all other cytokines; [c]p-values based on linear mixed-effect modeling. Figures plotted as mean and 95% confidence intervals. BD-2=beta defensin-2, FC=fold change, ICO=icotrokinra, IL=interleukin, PBO=placebo, W=week.

Early and robust reduction of PsO-related genes with ICO treatment in skin

- Downregulation observed as early as 8 weeks following crossover in PBO → ICO cohort
- At W24, gene expression level approached those seen in baseline (W0) non-lesional skin



[a]*p-values based on linear mixed-effect modeling. DEFB4A=gene that encodes human beta-defensin 2, ICO=icotrokinra, IL17A=interleukin-17A gene, IL17F=interleukin-17F gene, IL19=interleukin-19 gene, IL22=interleukin-22 gene, IL23A=interleukin-23A gene, PBO=placebo, W=week.*

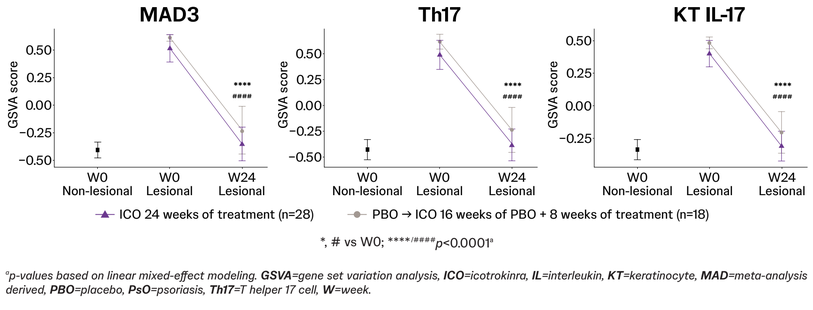
Early and robust normalization of PsO-related gene sets with ICO treatment by W24 in skin

- Downregulation observed as early as 8 weeks after crossover in the PBO → ICO cohort
- In the ICO cohort, gene set expression level was similar to baseline non-lesional skin at W24

Gene set for PsO lesional skin (meta-analysis derived)[3] — **MAD3**

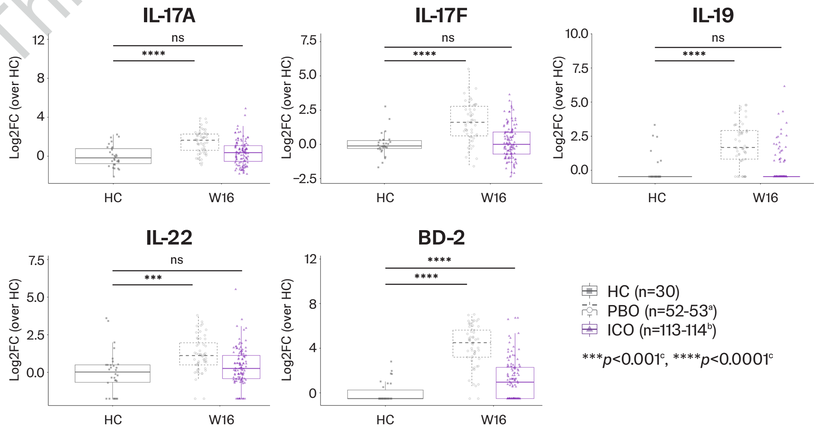
Gene set for IL-17-producing T cells[4,5] — **Th17**

Gene set for IL-17-stimulated keratinocytes[4,5] — **KT IL-17**



[a]*p-values based on linear mixed-effect modeling. GSVA=gene set variation analysis, ICO=icotrokinra, IL=interleukin, KT=keratinocyte, MAD=meta-analysis derived, PBO=placebo, PsO=psoriasis, Th17=T helper 17 cell, W=week.*

ICO normalized serum levels of IL-17A, IL-17F, IL-19, and IL-22 towards levels in HC by W16

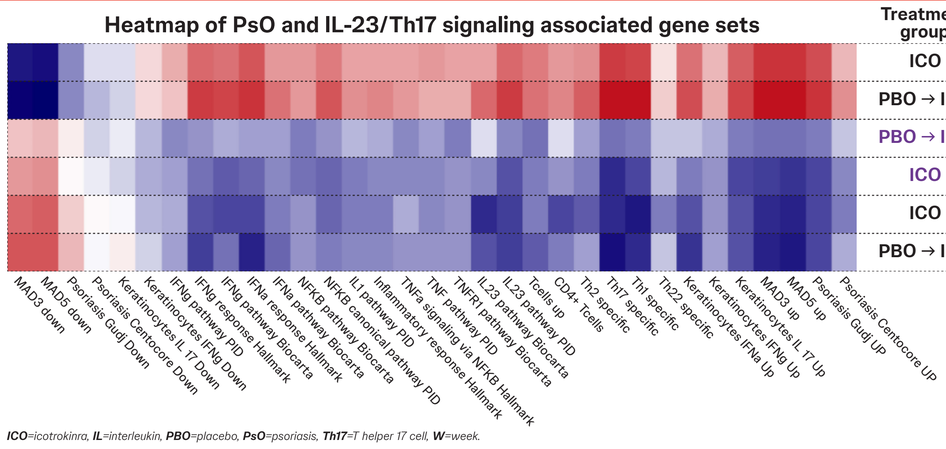


[a]*n=52 for IL-22, n=53 for all other cytokines; [b]n=113 for IL-22, n=114 for all other cytokines; [c]p-values based on two-sided Welch T test. Figures plotted as median and interquartile range. Each point denote individual log2FC over mean of log2concentration of HC samples. BD-2=beta defensin-2, FC=fold change, HC=healthy controls, ICO=icotrokinra, IL=interleukin, PBO=placebo, W=week.*

Early and sustained shift of PsO-related gene sets with ICO treatment in skin

- Downregulation observed as early as 8 weeks following crossover in PBO → ICO cohort
- Overall shift in expression of well-characterized PsO associated gene sets[3-7] toward baseline non-lesional state at W24

Heatmap of PsO and IL-23/Th17 signaling associated gene sets



Treatment group	Time points
ICO	Baseline lesional
PBO → ICO	Baseline lesional
PBO → ICO	W24 (8 weeks on treatment)
ICO	W24
ICO	Baseline non-lesional
PBO → ICO	Baseline non-lesional

ICO=icotrokinra, IL=interleukin, PBO=placebo, PsO=psoriasis, Th17=T helper 17 cell, W=week.

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