Robust Icotrokinra Systemic and Skin Pharmacodynamic Effects Versus Deucravacitinib in Patients With Moderate-to-Severe Plaque Psoriasis: Results From Phase 3, ICONIC-ADVANCE 1 Study

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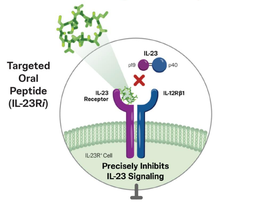
Background

- **Icotrokinra (ICO)** is the first and only targeted oral peptide for plaque psoriasis (PsO) that precisely binds the interleukin-23 receptor (IL-23R) and **inhibits IL-23 pathway signaling**[1]
- ICONIC-ADVANCE 1 (NCT06143878), a Phase 3 placebo (PBO)-controlled and deucravacitinib (Deucra) active comparator-controlled study of ICO in patients with moderate-to-severe plaque PsO, showed superior rates of skin clearance and a favorable safety profile[2]
  - Co-primary endpoints were met, with once daily ICO demonstrating significantly higher rates of skin clearance vs PBO at Week (W) 16
    - Investigator's Global Assessment (IGA) 0/1: 68% (ICO) vs 11% (PBO)
    - Psoriasis Area and Severity Index (PASI) 90: 55% (ICO) vs 4% (PBO)
  - ICO showed superior rates of skin clearance compared to Deucra
  - Similar adverse event rates between ICO and PBO were observed through W16, and no safety signals were identified through W24

Icotrokinra Blocks IL-23 From Binding to its Receptor



Inhibits IL-17A, IL-17F, IL-22, and IFNγ production

***IFN**=interferon, **IL-12Rβ1**=interleukin-12 receptor beta 1, **IL-17A**=interleukin-17A, **IL-17F**=interleukin-17F, **IL-23**=interleukin-23, **IL-23R**=interleukin-23 receptor, **IL-23Ri**=interleukin-23 receptor inhibitor.*

Objective

- **Evaluate ICO pharmacodynamic (PD) effects on disease markers, relative to both PBO and Deucra, through W24 of the ICONIC-ADVANCE 1 study**

Methods

ICONIC-ADVANCE 1 Study Design

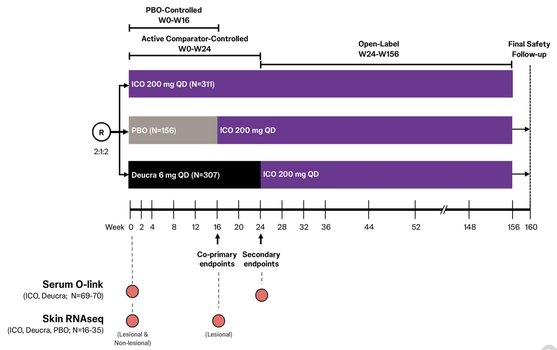
Moderate-to-severe plaque PsO (N=774)

Key inclusion criteria

- ≥18 years
- Plaque PsO for ≥26 weeks
- BSA ≥10%, PASI score ≥12, and IGA score ≥3
- Candidate for phototherapy or systemic treatment for plaque PsO
- Suitable candidate for Deucra per approved product labeling

Co-primary endpoints

- IGA score 0/1 & ≥2-grade improvement from baseline (IGA 0/1) and PASI 90 vs PBO at W16



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

ICONIC-ADVANCE 1 Biomarker Assessments and Analyses

Tissue PD:
- W0 non-lesional and lesional skin biopsies, and W16 lesional skin samples from 70 consenting participants of an optional sub-study treated with PBO, Deucra or ICO were analyzed
- Skin biopsy samples: Transcriptomic analysis using RNA sequencing

Systemic PD:
- W0 and W24 serum samples from a sub-cohort of 70 ICO- and 69 Deucra-treated participants were analyzed
- Serum samples from a separate healthy cohort of 22 subjects were included as a control group
- Serum samples: Analyzed for PsO-relevant biomarkers using O-link proteomic platform

Data Analysis:
- Comparison between ICO and Deucra vs PBO (skin PD) and between ICO vs Deucra (skin and serum PD): Linear mixed-effect modeling including effects for W0 levels, interaction between time and treatment, patient random effect, and other co-variates as appropriate
- Statistical significance: *p*-value ≤0.05 for individual biomarkers; adjusted *p*-value ≤0.05 and |logFC|>1 for differential gene expression cut-off threshold

***Deucra**=deucravacitinib, **ICO**=icotrokinra, **FC**=fold-change, **PBO**=placebo, **PD**=pharmacodynamics, **PsO**=psoriasis, **RNA**=ribonucleic acid, **W**=week.*

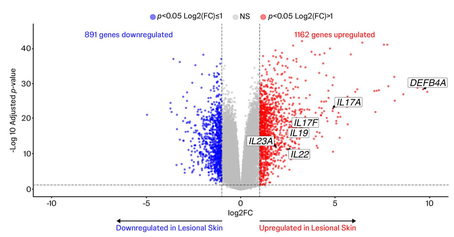
Key Takeaways

- **ICO demonstrated *substantial* PD effects, with levels of IL-23 pathway biomarkers for systemic and skin inflammation normalized towards healthy levels**
- **Skin transcriptomic data showed:**
  - **ICO reduced PsO skin and PD biomarkers at W16 compared to PBO**
  - **ICO normalized skin inflammation towards baseline non-lesional skin at W16**
  - **ICO elicited more robust effects on PsO and PD markers compared to Deucra**
- **Serum protein data demonstrated:**
  - **ICO reduced PsO serum biomarkers at W24 to a greater extent than Deucra**
- **These comprehensive biomarker findings are consistent with significant skin clearance[2] achieved with this first and only targeted oral peptide that precisely binds the IL-23R and inhibits the IL-23 pathway signaling. The more robust PD effects of ICO vs Deucra are consistent with superior clinical activity of ICO vs Deucra[2]**

Results

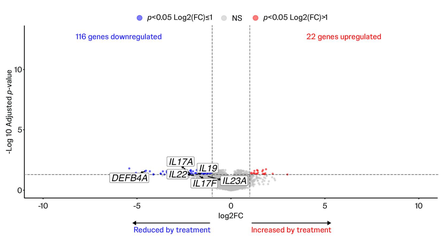
Baseline lesional and non-lesional skin exhibited highly differentiated transcriptomic profiles

- Differentially expressed genes included *IL17A, IL17F, IL19, IL22, IL23A,* and *DEFB4A,* which are related to PsO/IL-23 pathway



*Statistical models were determined for gene set based on simple linear mixed effects model based on limma-voom normalized log2 counts – Tissue (lesional vs non-lesional), p<0.05 for significance, and log2FC ≤1 and >1 for downregulation and upregulation cut-off, respectively. Based on all paired samples within the complete sample set; N=71 for lesional tissue, N=71 for non-lesional tissue. **DEFB4A**=gene that encodes human beta-defensin 2, **FC**=fold-change, **IL17A**=interleukin-17A gene, **IL17F**=interleukin-17F gene, **IL19**=interleukin-19 gene, **IL22**=interleukin-22 gene, **IL23A**=interleukin-23A gene, **NS**=not significant.*

Deucra elicited modest impact on PsO skin transcriptome (W16 lesional vs W0 lesional)



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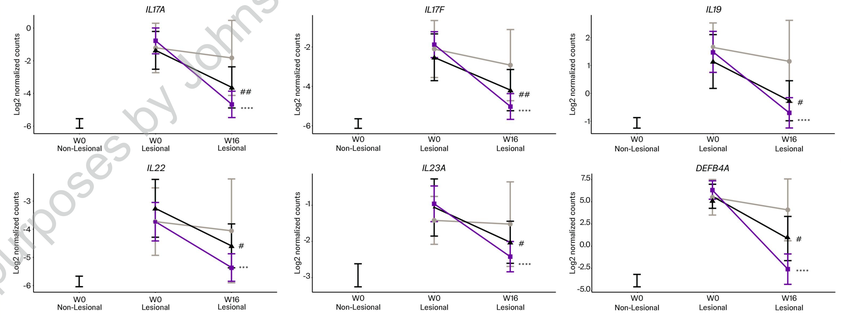
ICO reduced PsO-related gene expression in lesional skin towards non-lesional levels at W16

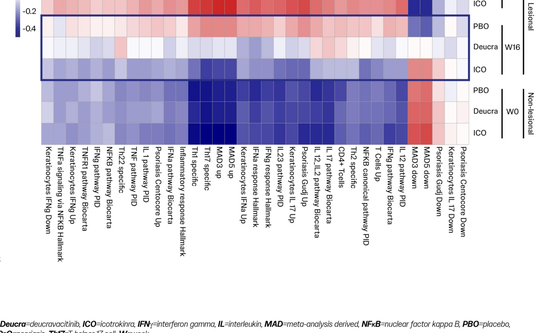
- ICO significantly reduced numerous PsO-related genes, including *IL17A, IL17F, IL19, IL22, IL23A,* and *DEFB4A*
- ICO-induced decrease of gene expression was more robust, as reflected by lower *p*-values, than the Deucra-induced decrease



significant change of ICO W16 vs W0, *significant change of Deucra W16 vs W0, #/^p-value <0.05, ##/^^p-value <0.01, ###/^^^p-value <0.001, ####/^^^^p-value <0.0001. **DEFB4A=gene that encodes human beta-defensin 2, **Deucra**=deucravacitinib, **ICO**=icotrokinra, **FC**=fold-change, **IL17A**=interleukin-17A gene, **IL17F**=interleukin-17F gene, **IL19**=interleukin-19 gene, **IL22**=interleukin-22 gene, **IL23A**=interleukin-23A gene, **NS**=not significant, **PBO**=placebo, **W**=week.*

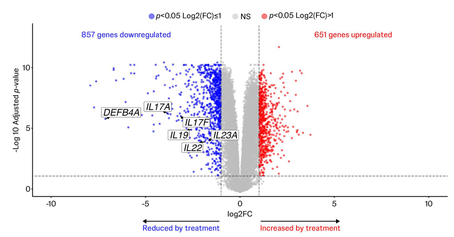
ICO induced transcriptional changes in lesional skin consistent with IL-23 pathway blockade and normalization of inflammation

- Transcriptomic profile of PsO-related gene sets[6,7] was highly differentiated between lesional and non-lesional skin at baseline
- ICO shifted PsO-relevant gene set expression toward that of non-lesional skin, while Deucra effects were modest



***CD4**=cluster of differentiation 4, **Deucra**=deucravacitinib, **ICO**=icotrokinra, **IFNγ**=interferon gamma, **IL**=interleukin, **MAD**=meta-analysis derived, **NFκB**=nuclear factor kappa B, **PBO**=placebo, **PID**=primary immunodeficiency, **PsO**=psoriasis, **Th17**=T helper 17 cell, **W**=week.*

ICO elicited robust impact on PsO skin transcriptome (W16 lesional vs W0 lesional)



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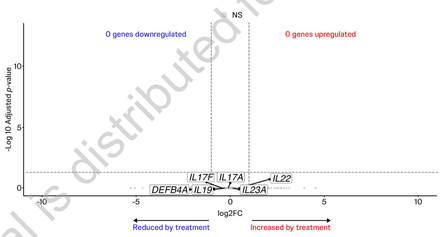
PBO elicited no impact on PsO skin transcriptome (W16 lesional vs W0 lesional)



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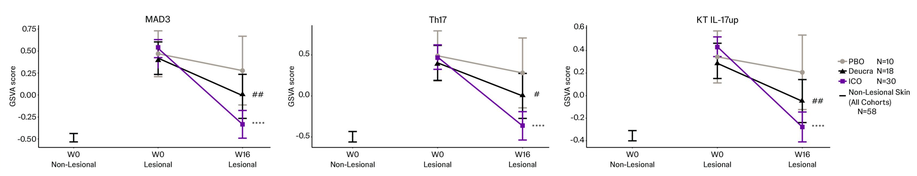
ICO reduced PsO- and Th17-related gene set expression in lesional skin at W16 to a greater degree than Deucra

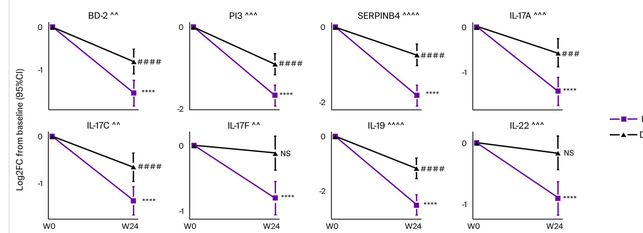
- ICO significantly reduced MAD3, Th17, and KT_IL17 gene sets[3-5] in lesional skin at W16 compared to baseline to a greater degree than PBO and Deucra and normalized towards non-lesional levels
- Comparison of gene set expression level at W16: significantly lower with ICO vs PBO ($p<0.001$) and ICO vs Deucra ($p<0.05$), with no significant difference between Deucra vs PBO ($p\geq0.05$)



significant change of ICO W16 vs W0, *significant change of Deucra W16 vs W0, #/^p-value <0.05, ##/^^p-value <0.01, ###/^^^p-value <0.001, ####/^^^^p-value <0.0001. **Deucra=deucravacitinib, **GVSA**=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 reduced serum PsO markers to a greater extent than Deucra

- ICO significantl y reduced serum PsO markers at W24
- Deucra significantly reduced some serum PsO markers from W0, although not IL-17F and IL-22, at W24



significant change of ICO W24 vs W0, *significant change of Deucra W24 vs W0, ^significant difference between treatments at W24, #/^p-value <0.05, ##/^^p-value <0.01, ###/^^^p-value <0.001, ####/^^^^p-value <0.0001. **BD-2=beta-defensin-2, **CI**=confidence interval, **Deucra**=deucravacitinib, **ICO**=icotrokinra, **IL**=interleukin, **NS**=not significant, **PI3**=peptidase inhibitor 3 (elafin), **SERPINB4**=serpin family B member 4, also known as squamous cell carcinoma antigen 2, **W**=week.*

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