Icotrokinra, the first targeted oral peptide that selectively blocks the interleukin-23 receptor, reduces systemic and tissue inflammatory burden in Ulcerative Colitis: Results from the ANTHEM-UC study

OP29

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Potential Conflicts of Interest

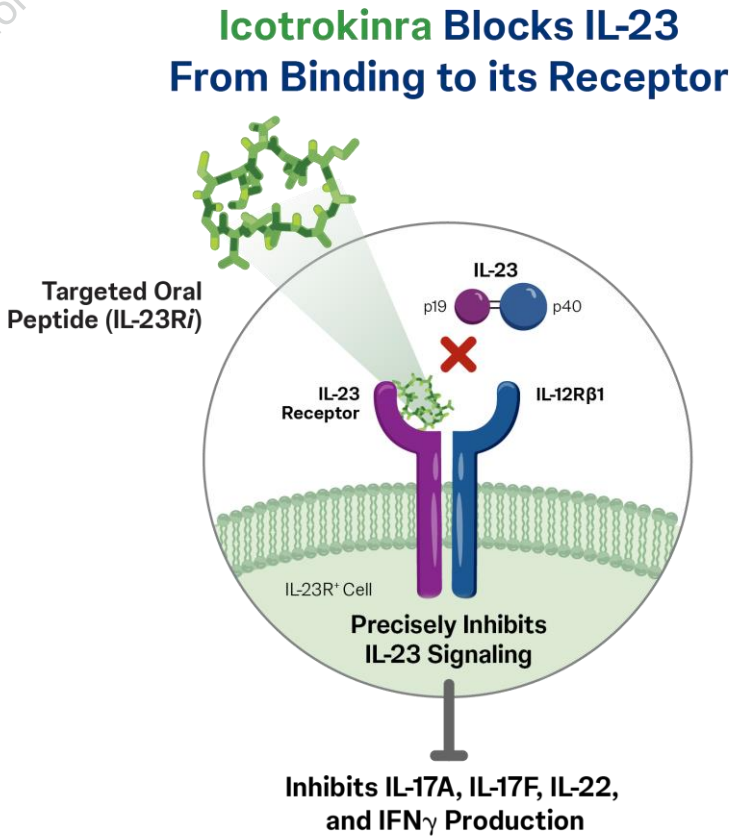
Professor Louis reports departmental educational and research grants from AbbVie, Celltrion, EG pharma, Falk, Fresenius-Kabi, Johnson & Johnson, Pfizer, Sandoz, and Takeda; fees for conferences, advisory boards, and consultancy from AbbVie, Arena, Biokuris, Bristol Myers Squibb, Celltrion, Falk, Ferring, Fresenius-Kabi, Galapagos, Johnson & Johnson, Lilly, Pfizer, Takeda, and Thabor

Background and Objective

Icotrokinra is a first-in-class investigational targeted oral peptide that precisely blocks the interleukin-23 (IL-23) receptor

All icotrokinra doses met the Week 12 primary endpoint[1] of ANTHEM-UC, a Phase 2b, randomised, double-blind, placebo-controlled, treat-through, dose-ranging study in adults with moderate to severe ulcerative colitis

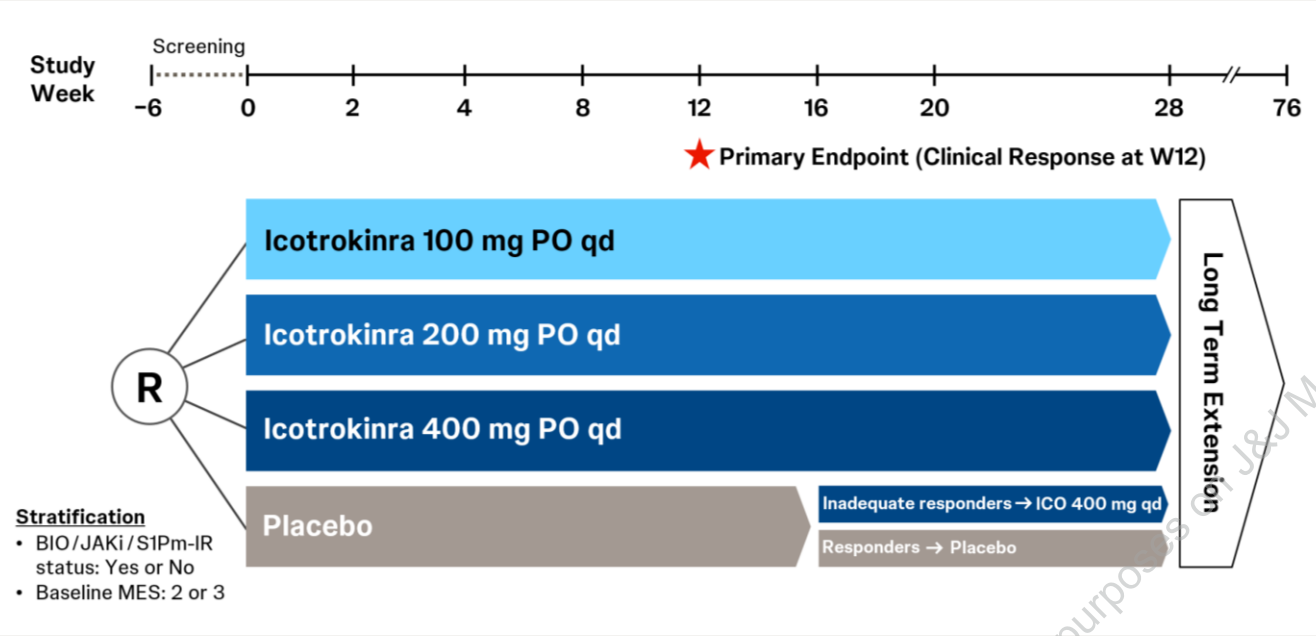
Icotrokinra also delivered clinically meaningful improvements across key secondary endpoints at Week 12, which were maintained or improved at Week 28[2]



Here we report the impact of icotrokinra treatment on systemic and tissue biomarkers of inflammatory burden in ANTHEM-UC study participants

1. Abreu MT, et al. United European Gastroenterol J. 2025 10;13(suppl 8):172-3.
2. Jairath V, et al. Am J Gastroenterol. 2025 120;10(suppl 2):S312.

ANTHEM-UC Design and Methods



Key Eligibility Criteria

- Diagnosed UC of ≥12 weeks duration
- Modified Mayo score of 5–9, inclusive
- Mayo endoscopic subscore (MES) ≥2 per central review
- Inadequate response/intolerance (IR) to CS, 6-MP, or AZA **OR** CS dependence **OR** IR to TNFα antagonists, ustekinumab, vedolizumab, JAK inhibitors, or S1P receptor modulators (BIO/JAKi/S1Pm-IR)

Clinical inflammatory biomarkers: C-reactive protein and faecal calprotectin

Systemic IL-23 pathway biomarkers: IL-22, IL-17A, and IL-17F

Tissue biomarkers: IL-23 pathway gene expression changes in colonic biopsies

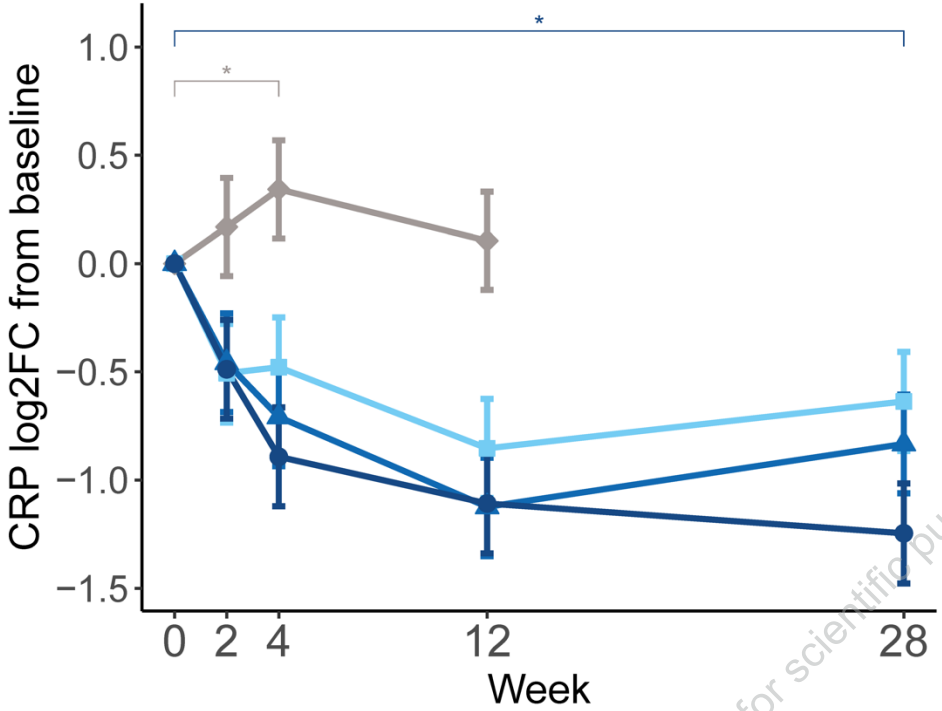
- At screening, biopsies were collected from the colon/rectum (at least 15–20 cm from the anal verge) in a representative area that was consistent with the severity of inflammation
- Subsequent biopsies from the same location were collected at Weeks 12 and 28

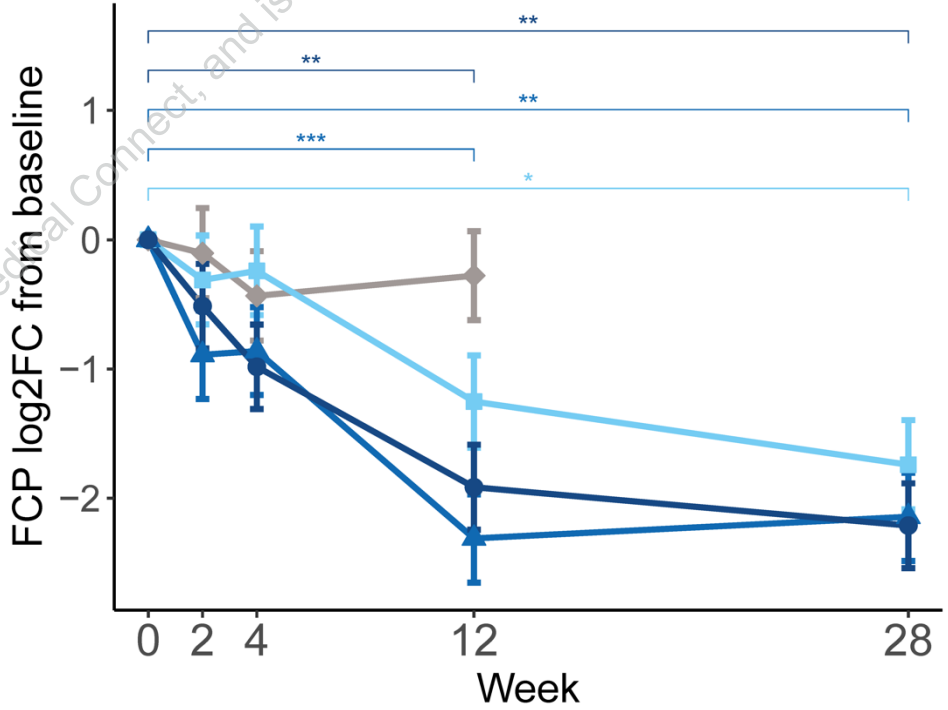
Statistical analyses of these biomarkers were not controlled for multiple comparisons

Demographics and Baseline Disease Characteristics

	Placebo	Icotrokinra 100 mg qd	Icotrokinra 200 mg qd	Icotrokinra 400 mg qd	Total
Full analysis set, n	63	64	62	63	**252**
Age, years, mean (SD)	38.3 (13.8)	45.8 (14.6)	41.8 (14.6)	40.6 (14.8)	**41.6 (14.7)**
Sex, male, n (%)	35 (55.6%)	40 (62.5%)	32 (51.6%)	40 (63.5%)	**147 (58.3%)**
Race, White, n (%)	44 (69.8%)	45 (70.3%)	39 (62.9%)	42 (66.7%)	**170 (67.5%)**
UC disease duration, years, mean (SD)	8.3 (8.1)	7.4 (6.1)	7.8 (7.5)	7.6 (7.6)	**7.8 (7.3)**
Extensive disease, n (%)	27 (42.9%)	23 (35.9%)	23 (37.1%)	29 (46.0%)	**102 (40.5%)**
Modified Mayo score [max = 9], mean (SD)	6.75 (1.231)	6.55 (1.296)	6.75 (1.386)	6.49 (1.401)	**6.63 (1.327)**
Mayo endoscopic subscore of 3 (severe), n (%)	36 (57.1%)	38 (59.4%)	37 (59.7%)	37 (58.7%)	**148 (58.7%)**
Faecal calprotectin, mg/kg, median [IQR]	1467.0 [420.5; 3622.0]	1433.3 [698.0; 3121.2]	2467.0 [646.4; 4599.6]	1421.3 [584.6; 4978.6]	**1523.0 [587.0; 3816.7]**
CRP, mg/L, median [IQR]	3.0 [0.9; 7.0]	3.0 [1.1; 6.7]	5.3 [1.5; 11.3]	4.0 [1.5; 8.1]	**3.6 [1.3; 8.1]**

Clinical Inflammatory Biomarkers





Placebo
n = 63

Icotrokinra 100 mg qd
n = 64

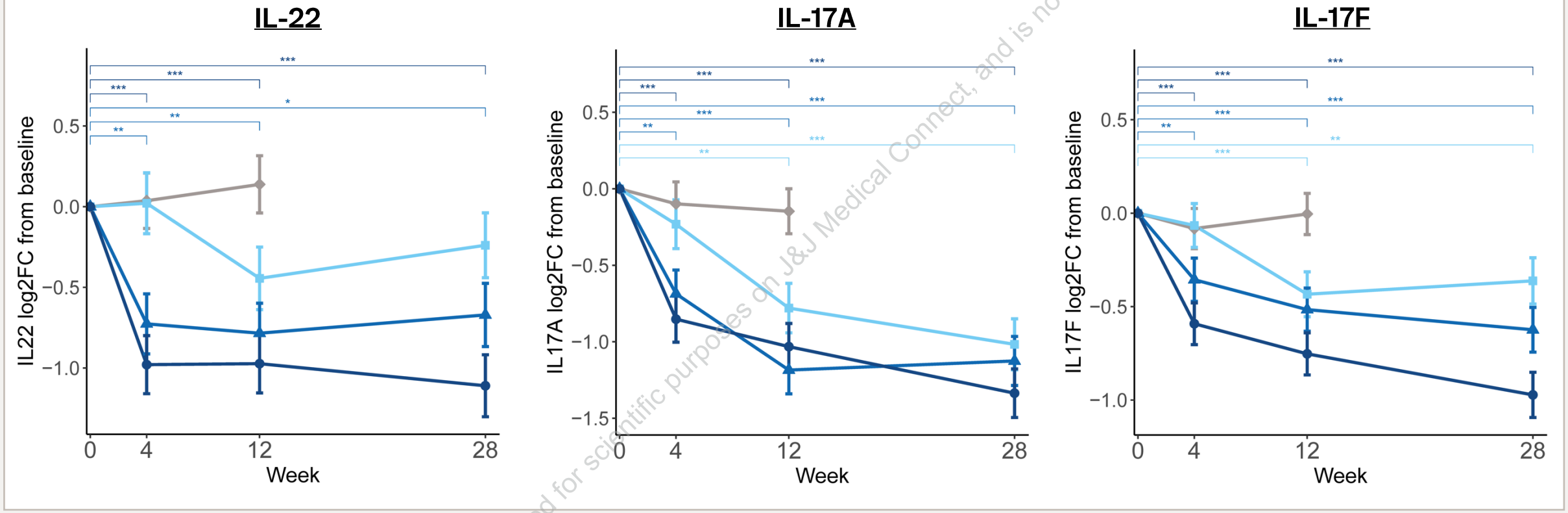
Icotrokinra 200 mg qd
n = 62

Icotrokinra 400 mg qd
n = 63

Nominal *p< 0.05, **p<0.001, ***p<0.001 for log2 fold change from baseline

Plots track mean values (estimated marginal means) using a linear mixed effect model that accounts for treatment*time interaction, age, and sex, with subject as a random effect.
Error bars are model-based standard errors.

Systemic IL-23 Pathway Biomarkers



Placebo
n = 44–58

Icotrokinra 100 mg qd
n = 44–50

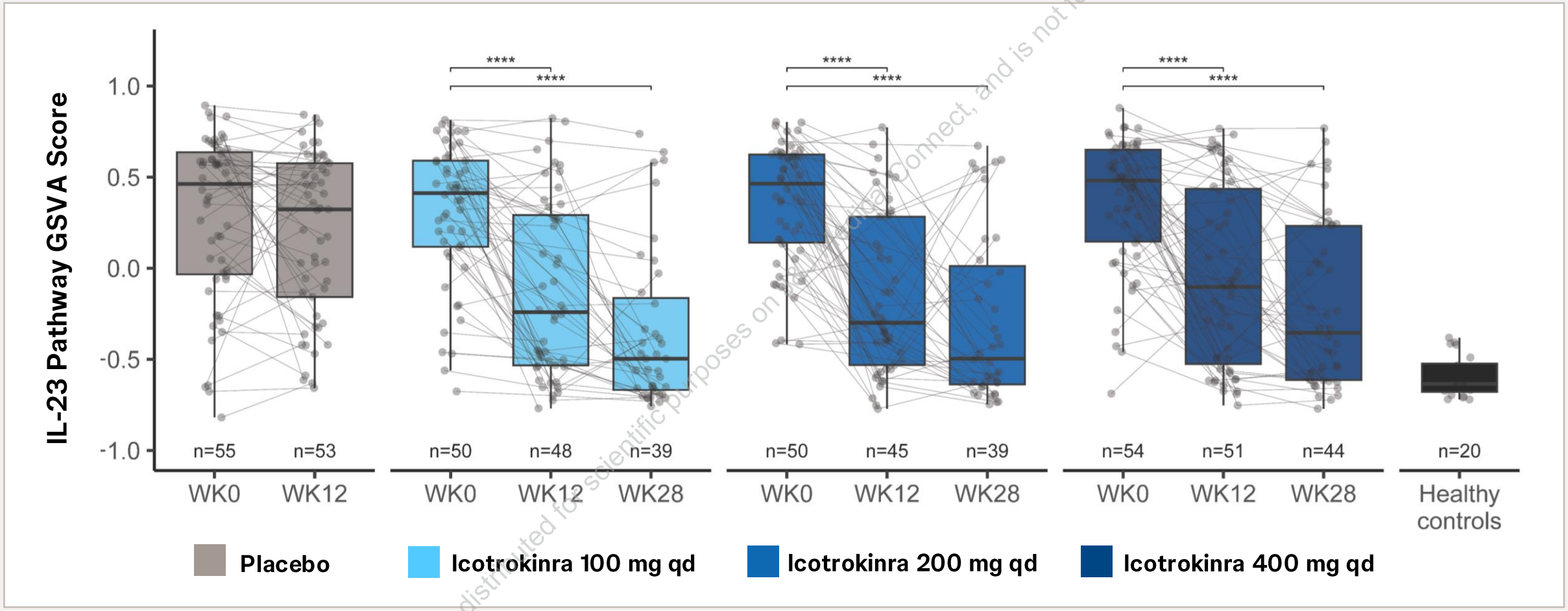
Icotrokinra 200 mg qd
n = 44–49

Icotrokinra 400 mg qd
n = 46–53

Nominal *p< 0.05, **p<0.001, ***p<0.001, ****p<0.0001 for log2 fold change from baseline

Plots track mean values (estimated marginal means) using a linear mixed effect model that accounts for treatment*time interaction, age, and sex, with subject as a random effect.
Error bars are model-based standard errors.

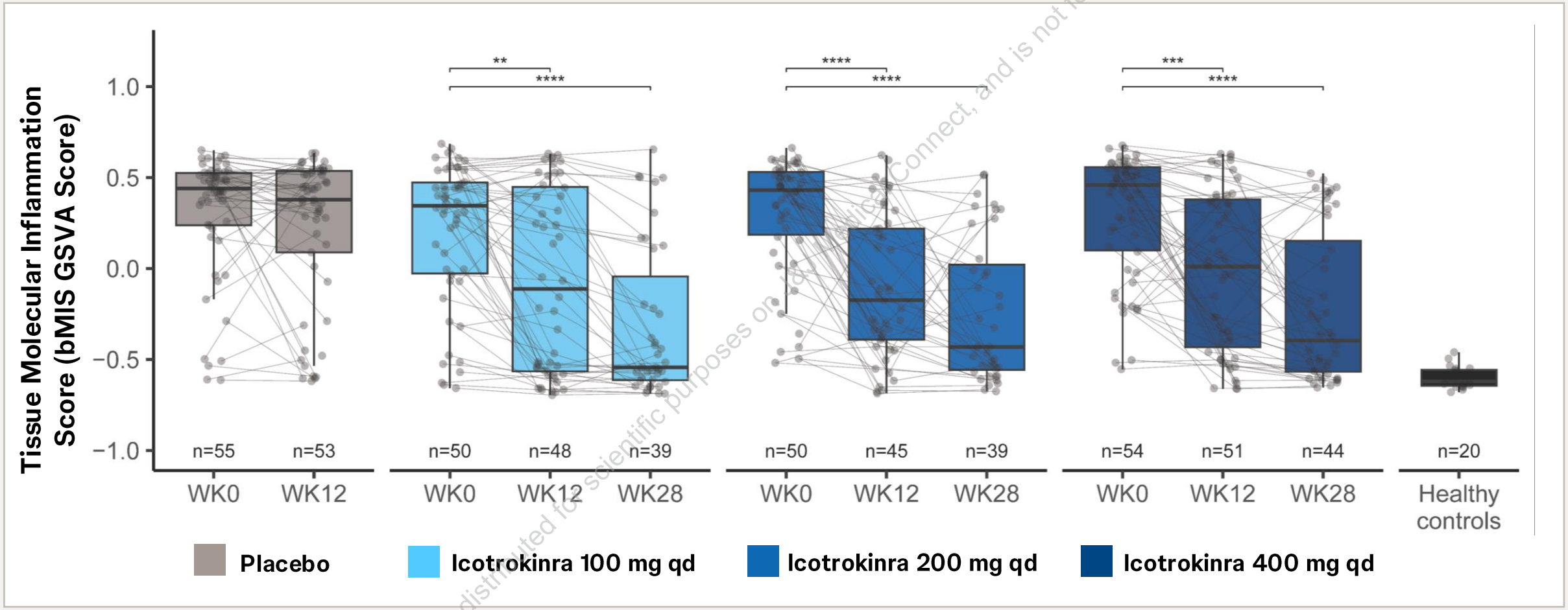
Tissue IL-23 Pathway Activation



Nominal ****p<0.0001

Quantification of IL-23 pathway gene enrichment score using gene set variation analysis (GSVA) at the indicated time points after placebo or icotrokinra treatment. GSVA scores are depicted and compared at Week 0 and Week 12 or Week 28 with a t-test. Error bars are 95% confidence intervals. Data from healthy controls were generated from commercially obtained colonic biopsies.

Tissue Inflammatory Burden

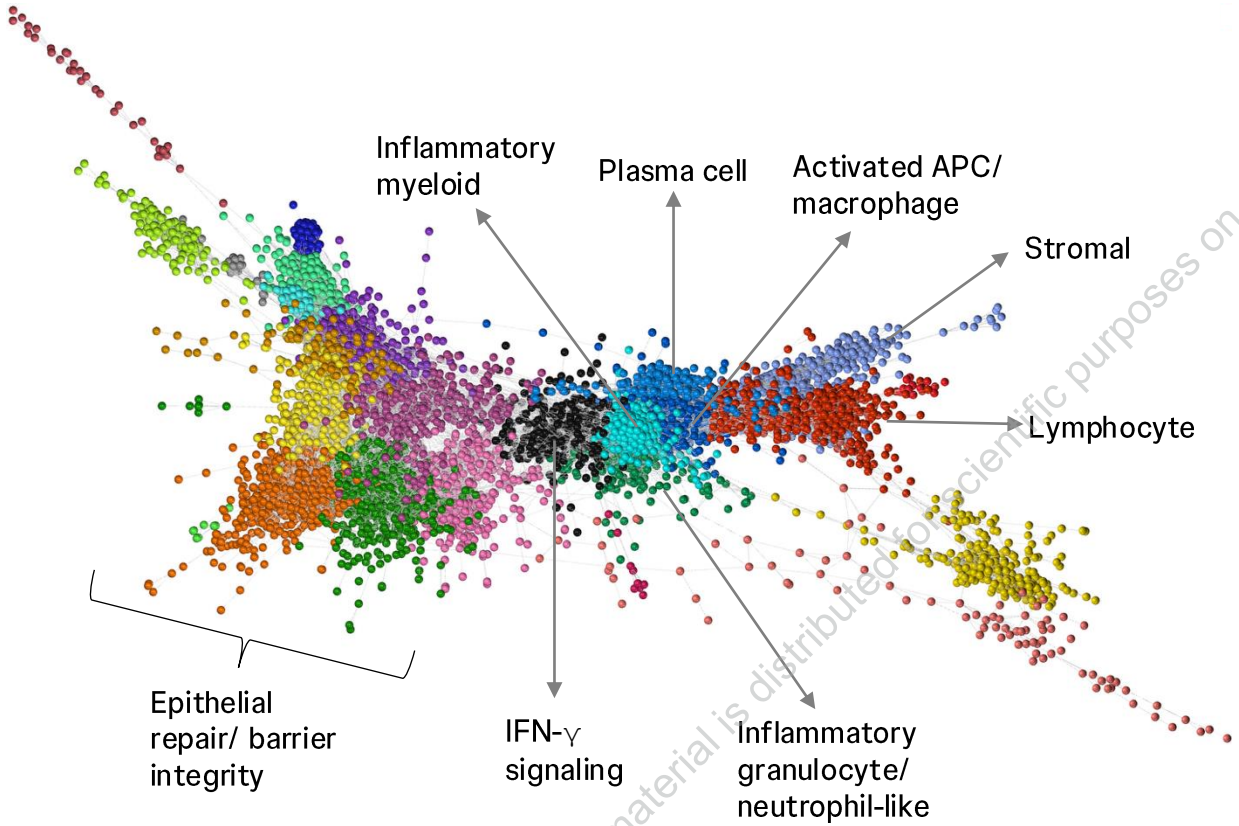


Nominal **p<0.01, ***p<0.001, ****p<0.0001

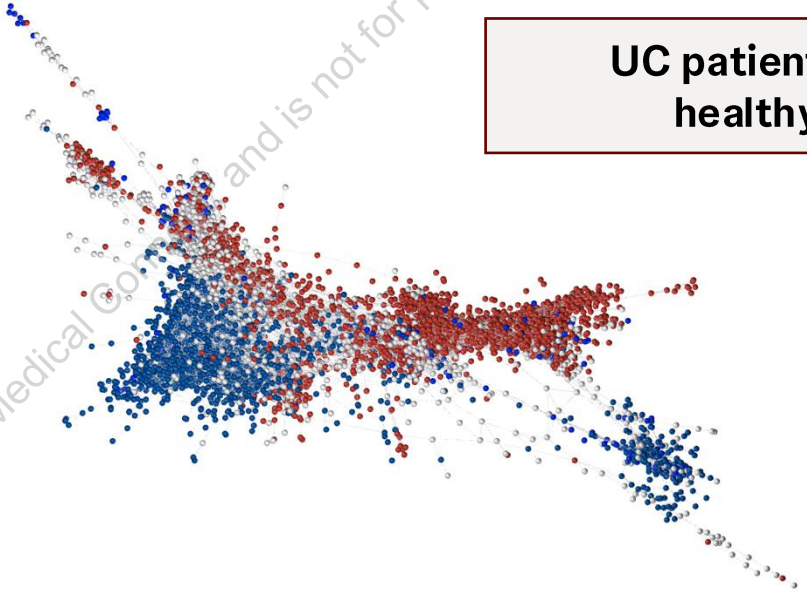
Quantification of biopsy molecular inflammation score (bMIS) using gene set variation analysis (GSVA) at the indicated time points after placebo or icotrokinra treatment. GSVA scores are depicted and compared at Week 0 and Week 12 or Week 28 with a t-test. Error bars are 95% confidence intervals. Data from healthy controls were generated from commercially obtained colonic biopsies.

Tissue Transcriptome: Impact of Icotrokinra Treatment

Gene correlation network analysis identifies distinct cell clusters in colonic biopsy transcriptomic data



UC patients relative to healthy controls

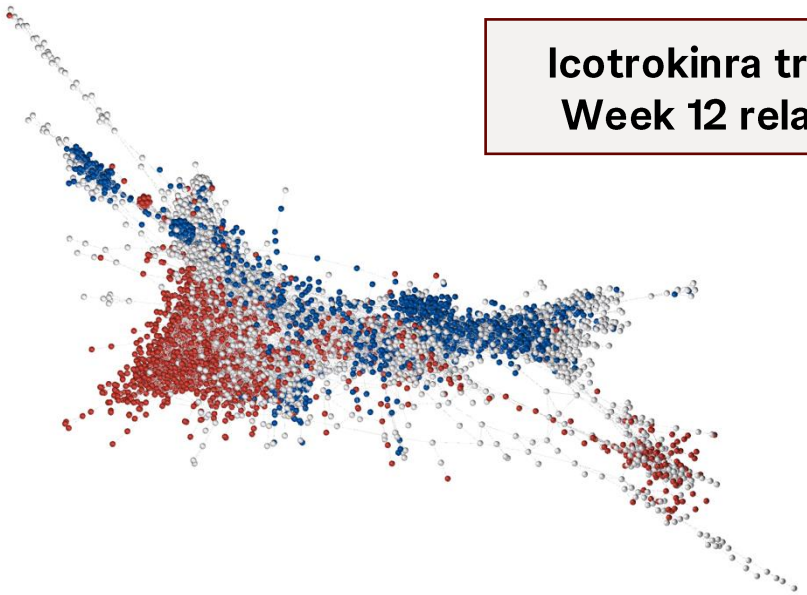


Downregulated in UC samples

Unchanged in UC samples

Upregulated in UC samples

Icotrokinra treatment effect: Week 12 relative to Week 0



Upregulated with icotrokinra

Unchanged with icotrokinra

Downregulated with icotrokinra

Data from healthy controls were generated from commercially obtained colonic biopsies.

Abs(logFC >0)
FDR < 0.05

Conclusions

- Precisely blocking the IL-23 receptor with once-daily icotrokinra reduced IL-23–mediated inflammatory burden in the systemic circulation and in tissue of patients with ulcerative colitis
- Icotrokinra induced transcriptional changes that are consistent with dampening of IL-23–driven inflammation and normalisation of the tissue transcriptome
- All once-daily doses of icotrokinra attenuated systemic and tissue inflammation; greater reduction of systemic inflammatory burden was observed with the 200 mg and 400 mg doses

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