Icotrokinra, a Targeted Oral Peptide That Selectively Blocks the Interleukin-23 Receptor, for the Treatment of Moderate-to-Severe Plaque Psoriasis: Results Through Week 24 of the Phase 3, Randomized, Double-Blind, Placebo-Controlled ICONIC-LEAD Trial

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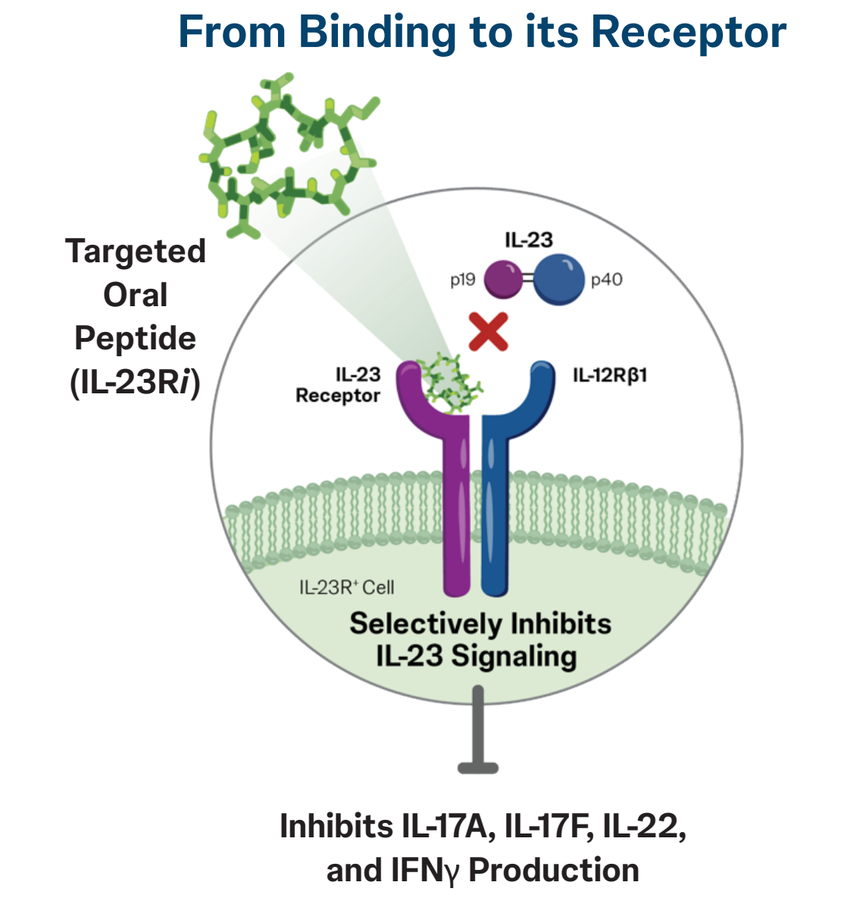
Key Takeaways

In ICONIC-LEAD, among the first pivotal trials evaluating the novel targeted oral peptide ICO in adults and adolescents with moderate-to-severe plaque PsO:

- ✓ ICO demonstrated *significantly higher rates of clear/almost clear skin and scalp* disease and *PsO symptom relief* than PBO at W16
- ✓ ICO demonstrated *separation from PBO as early as W4, with increasing response rates through W24*
- ✓ *Rates of AEs were similar* between the ICO and PBO groups
- ✓ *No safety signal* was identified through W24

Background

- Patients with moderate-to-severe plaque psoriasis (PsO) are generally limited to injectable therapies to achieve high-level efficacy with a favorable safety profile
- Icotrokinra (ICO) is a first-in-class, targeted oral peptide that:
  - Selectively binds the interleukin (IL)-23 receptor and inhibits IL-23 pathway signaling[1]
  - Demonstrated significant skin clearance and no safety signals through 1 year in Phase 2 PsO studies[2,3]
  - Is being evaluated in Phase 3 studies in adults and adolescents with moderate-to-severe plaque PsO (ICONIC-LEAD)



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

Objectives

Here we report key clinical and patient-reported outcomes (PROs) and safety-related findings from the pivotal ICONIC-LEAD study through Week (W) 24

ICONIC-LEAD study design

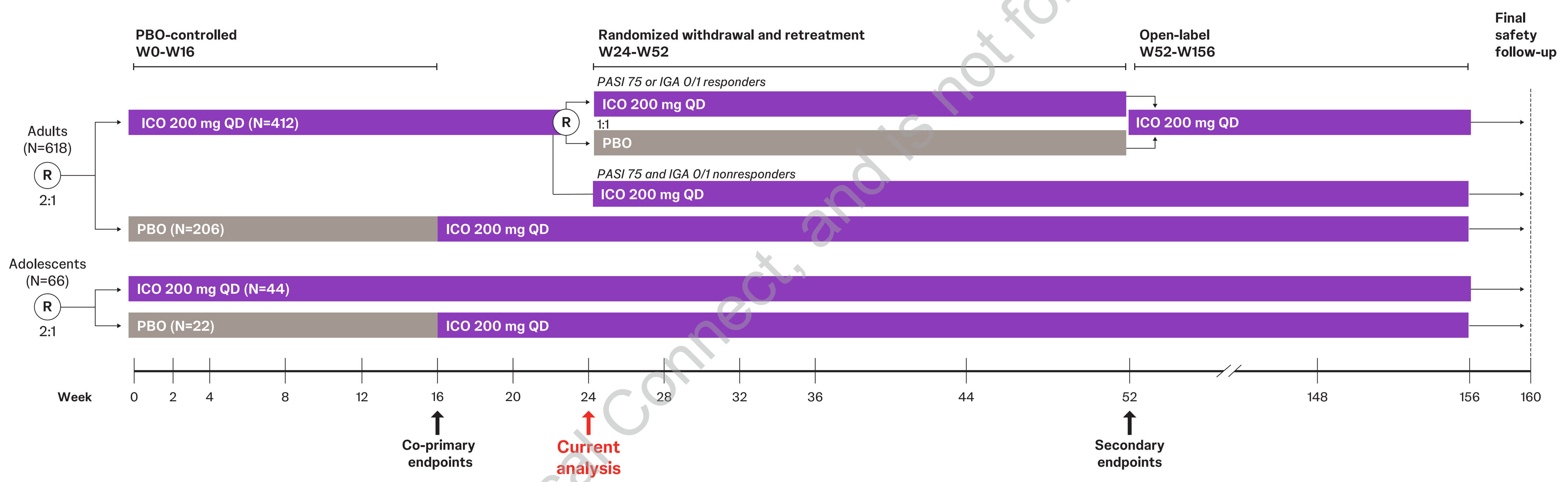
Moderate-to-severe plaque PsO (N=684)

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

Endpoints

Co-primary endpoints:
- IGA 0/1 at W16
- PASI 90 at W16

Key secondary endpoints:
- **Clinical outcomes** (PASI 75/90/100, IGA 0) at W4, W8, and/or W16
- **PROs** (≥4-point improvement from baseline in PSSD Itch, PSSD Symptom 0) at W4, W8, and/or W16
- **Scalp PsO** (ss-IGA 0/1) at W16


PBO-controlled W0-W16
Randomized withdrawal and retreatment W24-W52
Open-label W52-W156
Final safety follow-up
Adults (N=618)
R
2:1
ICO 200 mg QD (N=412)
PASI 75 or IGA 0/1 responders
ICO 200 mg QD
1:1
PBO
PASI 75 and IGA 0/1 nonresponders
ICO 200 mg QD
PBO (N=206)
ICO 200 mg QD
Adolescents (N=66)
ICO 200 mg QD (N=44)
PBO (N=22)
Week
0 2 4 8 12 16 20 24 28 32 36 44 52 148 156 160
Co-primary endpoints
Current analysis
Secondary endpoints

*Participants with the following intercurrent events were considered as nonresponders: discontinued study drug due to a lack of efficacy or AE of worsening PsO or initiated prohibited medication that could impact PsO. After accounting for these intercurrent events, nonresponder imputation was applied to participants with missing data. **AE**=adverse event, **IGA 0/1**=IGA score of 0 (clear)/1 (almost-clear) and a ≥2-grade improvement, **PASI 75/90/100**=reduction from baseline of 75%/90%/100% in the PASI score, **PBO**=placebo, **PSSD**=Psoriasis Symptom and Sign Diary, **QD**=once daily, **R**=randomization, **ss-IGA**=scalp-specific Investigator's Global Assessment, **ss-IGA 0/1**=ss-IGA score of 0 (clear)/1 (almost clear) and a ≥2-grade improvement from baseline.*

Results

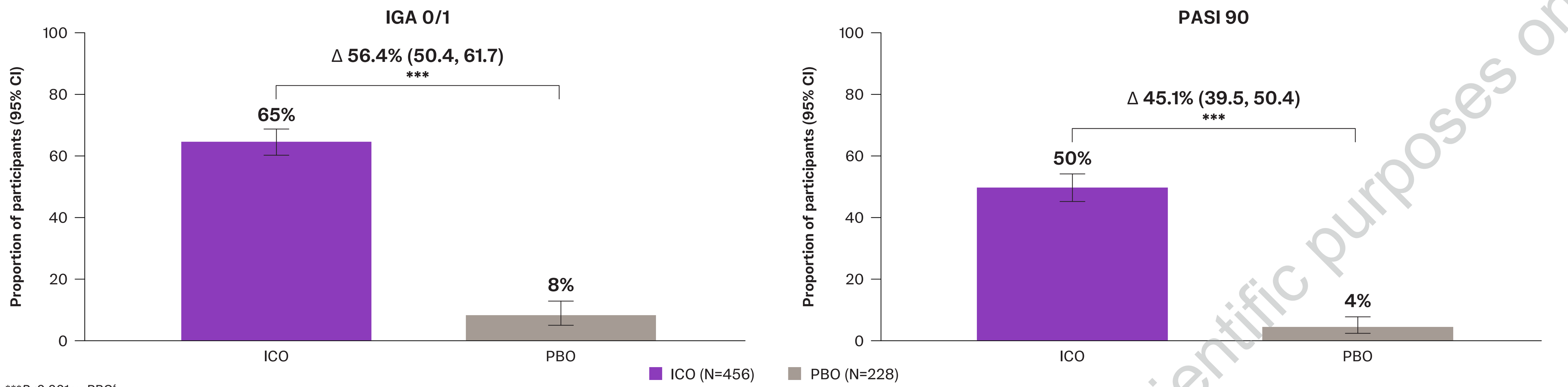
Baseline characteristics were similar between groups

- Overall, 5% of participants (ICO: 4%; PBO: 6%) discontinued prior to W16[a]

Baseline characteristics	ICO 200 mg QD (N=456)	PBO (N=228)
Demographic characteristics		
Age, year, mean (SD)	42.4 (16.3)	43.2 (16.6)
Adolescent cohort, year	15.0 (1.8)	15.0 (1.5)
Male	64%	68%
White	72%	72%
BMI, kg/m², mean (SD)[b]	29.2 (6.9)	29.3 (7.0)
Disease characteristics		
Psoriasis disease duration, year, mean (SD)	17.3 (13.9)	16.6 (12.7)
% BSA with psoriasis, mean (SD)	24.6 (14.3)	27.1 (16.2)
IGA score		
Moderate (3)	75%	76%
Severe (4)	25%	24%
PASI (0-72), mean (SD)	19.4 (7.1)	20.8 (8.1)
PsO involving the scalp area		
ss-IGA score[c]		
Moderate (3)	59%	51%
Severe (4)	17%	22%
Prior treatment for PsO		
Phototherapy (PUVA and UVB)	30%	29%
Systemic therapy[d]	72%	71%
Biologic therapy[e]	32%	37%

*[a]Among the participants who discontinued prior to W16 (ICO: n=19 [4%]; PBO: n=14 [6%]), the most common reasons for discontinuation were withdrawal by participant in the ICO group (n=8 [2%]) and lack of efficacy in the PBO group (n=8 [4%]). [b]ICO: N=455; PBO: N=227. [c]ICO: N=451; PBO: N=227. [d]Conventional nonbiologic systemics, novel nonbiologic systemics, 1,25-vitamin D3 and analogues, phototherapy, and biologics. [e]Adalimumab, alefacept, briakinumab, brodalumab, certolizumab pegol, efalizumab, etanercept, guselkumab, infliximab, ixekizumab, natalizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab. **BMI**=body mass index, **PUVA**=psoralen plus ultraviolet A, **SD**=standard deviation, **UVB**=ultraviolet B.*

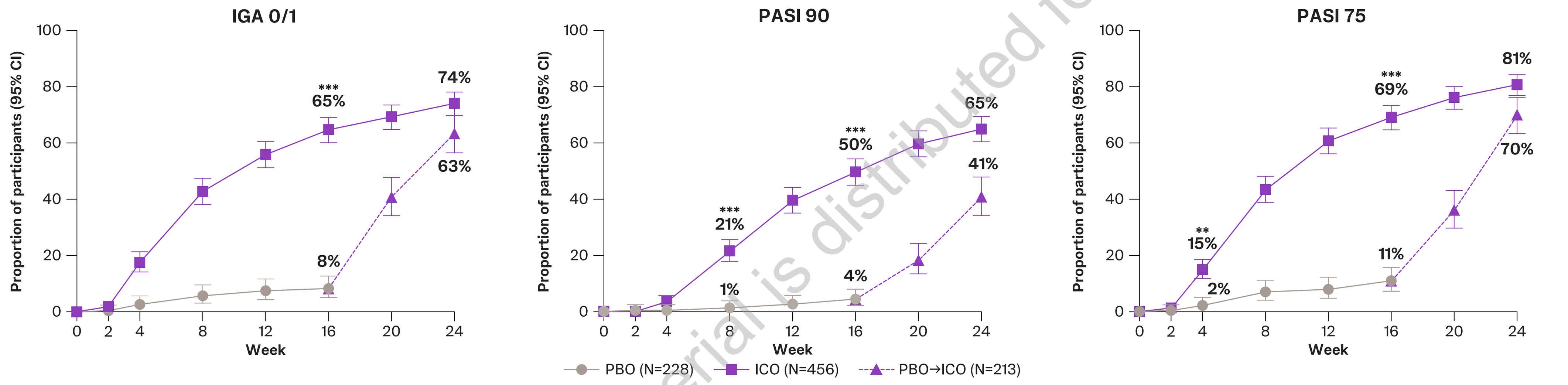
ICO demonstrated *significantly higher rates of IGA 0/1 and PASI 90* vs PBO at W16 (co-primary endpoints)



***P<0.001 vs PBO[f]

*[f]P values were calculated based on Cochran-Mantel-Haenszel chi-square test stratified by age group, baseline weight category (adults only), and geographic region. **CI**=confidence interval.*

ICO demonstrated *early separation* from PBO; rates of clear/almost clear skin increased through W24

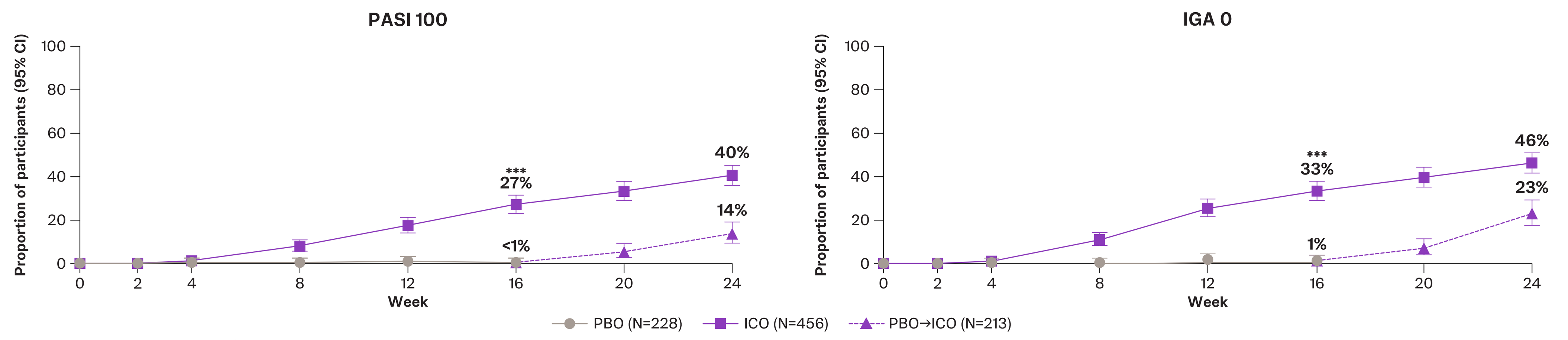


,*Multiplicity-adjusted P<0.01, P<0.001 vs PBO[g]

[g]P values were calculated based on Cochran-Mantel-Haenszel chi-square test stratified by age group, baseline weight category (adults only), and geographic region, if applicable.

ICO demonstrated significantly higher rates of *complete skin clearance* vs PBO

- ICO showed separation from PBO as early as W8; rates of complete skin clearance increased through W24

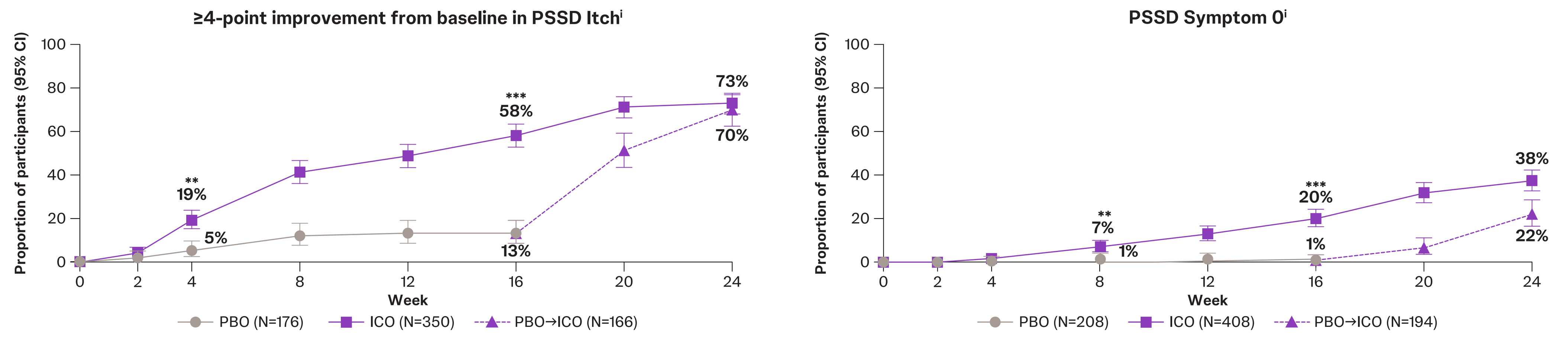


***Multiplicity-adjusted P<0.001 vs PBO[h]

[h]P values were calculated based on Cochran-Mantel-Haenszel chi-square test stratified by age group, baseline weight category (adults only), and geographic region.

Significantly higher proportions of ICO- vs PBO-treated participants reported *meaningful improvements in PsO itch*

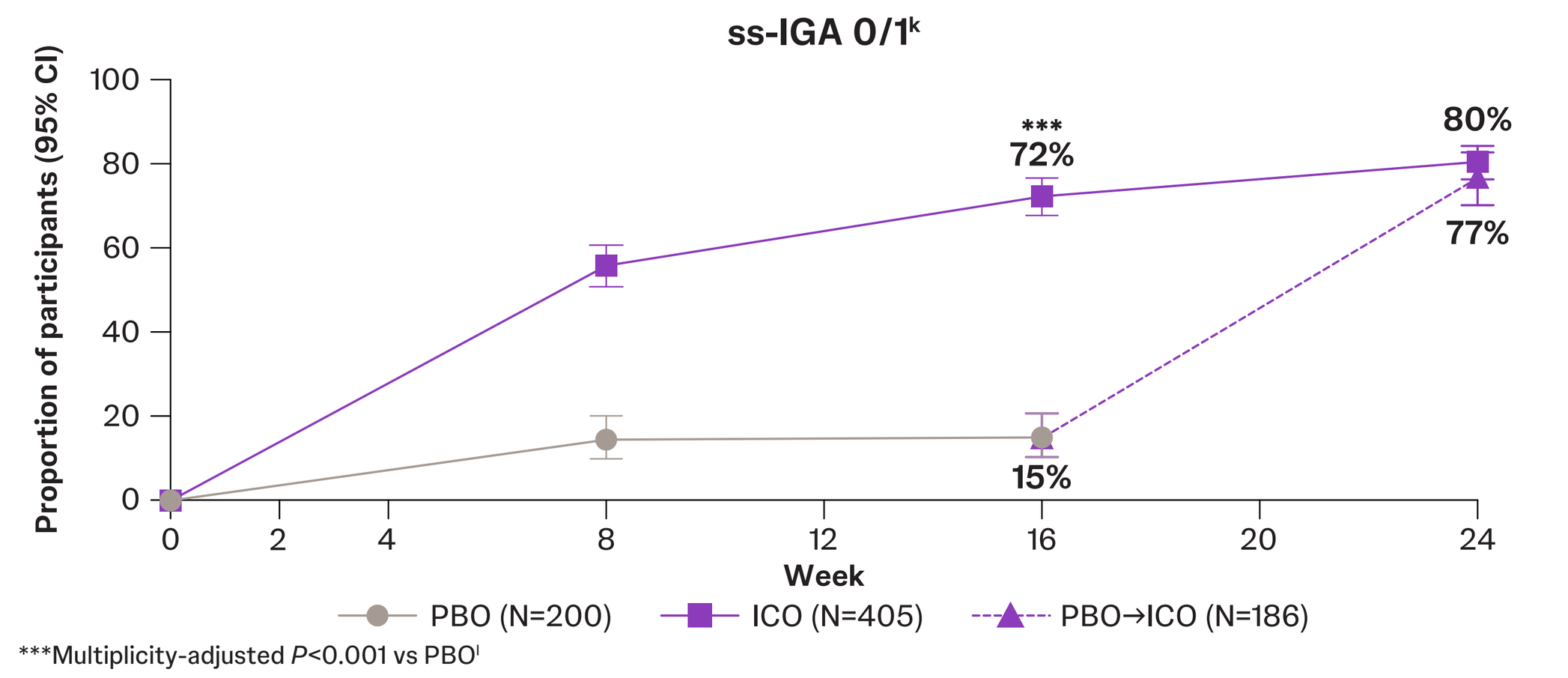
- ICO demonstrated early separation from PBO on improving itch and resolving symptoms; response rates increased through W24



**, ***Multiplicity-adjusted P<0.01 , P<0.001 vs PBO[j]

[i]Among participants with a baseline PSSD Itch score ≥4 or PSSD Symptom score >0. [j]P values were calculated based on Cochran-Mantel-Haenszel chi-square test stratified by age group, baseline weight category (adults only), and geographic region, if applicable. Fisher's exact test was used for PSSD Symptom 0 at W8.

ICO demonstrated significantly higher rates of *clear/almost clear scalp PsO* vs PBO



***Multiplicity-adjusted P<0.001 vs PBO[l]

[k]Among participants with a baseline ss-IGA score ≥2. [l]P values were calculated based on Cochran-Mantel-Haenszel chi-square test stratified by age group, baseline weight category (adults only), and geographic region.

Adverse event rates were generally similar between groups through W16

- Through W24 of ICO treatment, the most commonly reported AEs were similar to those observed through W16 and no safety signal emerged

	ICO 200 mg QD (N=456)	PBO (N=228)
Safety through W16		
Mean weeks of follow-up	15.9	15.8
Any AE	225 (49%)	112 (49%)
Most common AEs (≥5%)		
Nasopharyngitis	31 (7%)	15 (7%)
Upper respiratory tract infection	30 (7%)	16 (7%)
SAE[m]	6 (1%)	6 (3%)
Infection	107 (23%)	51 (22%)
Serious infection	1 (<1%)	0
AE leading to discontinuation[n]	6 (1%)	1 (<1%)
Gastrointestinal AE	26 (6%)	13 (6%)
Active TB	0	0
Malignancy[o]	2 (<1%)	0

*[m]SAEs through W16 included acute cholecystitis, concussion, craniofacial fracture, pelvic fracture, psoriasis, and hypertensive urgency in the PBO group; and adenocarcinoma of the colon, prostate cancer, pancreatitis, bacterial gastroenteritis (serious infection), arthralgia, and subarachnoid hemorrhage in the ICO group. [n]AEs leading to discontinuation through W16 included blood glucose increased in the PBO group; and adenocarcinoma of the colon, prostate cancer, hypertriglyceridemia, subarachnoid hemorrhage, erectile dysfunction, and psoriasis in the ICO group. [o]Malignancies reported were adenocarcinoma of the colon (n=1 in a participant who had a history of smoking; the participant reported mild gastroenteritis during screening, and severe colitis starting on study day 7, and severe ileus on day 14 leading up to the diagnosis of grade 3 adenocarcinoma of the colon on day 19) and prostate cancer (n=1 in a 62-year-old male, former smoker [30 pack years], with a family history [brother] of prostate cancer, and an elevated prostate-specific antigen level prior to baseline was diagnosed with grade 1 prostate cancer on study day 48 following a positive biopsy). **SAE**=serious adverse event, **TB**=tuberculosis.*

REFERENCES: 1. Fourie AM, et al. *Sci Rep.* 2024;14:17515. **2.** Bissonnette R, et al. *N Engl J Med.* 2024;390:510-21. **3.** Ferris LK, et al. *J Am Acad Dermatol.* Published online November 14, 2024. doi: 10.1016/j.jaad.2024.10.076.
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