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ORIGINAL ARTICLE

Targeted Oral Peptide Icotrokinra for Psoriasis Involving High-Impact Sites

Melinda Gooderham, M.D., M.Sc.,[1] Edward Lain, M.D.,[2] Robert Bissonnette, M.D.,[3] Yu-Huei Huang, M.D.,[4] Charles W. Lynde, M.D.,[5,6] Matthias Hoffmann, M.D.,[7] Eingun James Song, M.D.,[8] Oliver Weirich, M.D.,[9] Raul Hernan Gabriel Ceitlin, M.D.,[10] Jessica H. Rubens, M.D.,[11] Amy M. DeLozier, Dr.P.H.,[11] Takayuki Ota, M.D., Ph.D.,[11] Ming-Chun Hsu, Ph.D.,[11] Shu Li, Ph.D.,[11] Cynthia M. C. DeKlotz, M.D.,[11] Fabio Nunes, M.D.[11] and Richard B. Warren, M.D., Ph.D.[12]

Abstract

BACKGROUND Plaque psoriasis involving high-impact sites is difficult to treat. Icotrokinra, a targeted oral peptide that selectively binds interleukin-23 receptors, is a new treatment being investigated for this condition.

METHODS This phase 3, double-blind, placebo-controlled trial randomly assigned participants 12 years of age and over with plaque psoriasis {with a body surface area ≥1%; an Investigator's Global Assessment (IGA) score ≥2 [clear (0), minimal (1), mild (2), moderate (3), and severe (4)] for overall skin; and at least moderate psoriasis involving the scalp, genitalia, and/or hands and feet} to receive either icotrokinra 200 mg daily or placebo in a 2:1 ratio. The primary end point at week 16 was the proportion of participants achieving an overall IGA score of 0 or 1 and an improvement of 2 points or more from baseline (IGA score of 0 or 1), reported as the between-group difference adjusted for high-impact site involvement, geographic region, and body surface area category using Mantel–Haenszel weights. Absent/clear or minimal/almost clear scalp, genital, and/or hand and foot psoriasis at 16 weeks were secondary end points. Adverse events were recorded.

RESULTS The trial randomly assigned 311 participants (icotrokinra, n=208; placebo, n=103) with scalp (n=252: icotrokinra, n=167; placebo, n=85), genital (n=140: icotrokinra, n=98; placebo, n=42), and/or hand and foot (n=71: icotrokinra, n=48; placebo, n=23) psoriasis. The proportions of participants achieving an IGA score of 0 or 1 in the icotrokinra and placebo groups were 56.7% and 5.8%, respectively [adjusted difference, 51.1 percentage points; 95% confidence interval (CI), 42.1 to 58.8; P<0.001]. The proportions of icotrokinra-treated and placebo-treated participants achieving absence/clear or minimal/almost clear high-impact site psoriasis were as follows: scalp, 65.9% and 10.6% (difference, 55.5 percentage points; 95% CI, 44.8 to 64.4; P<0.001); genitalia, 76.5% and 21.4% (difference, 55.4 percentage points; 95% CI, 39.1 to 68.0; P<0.001); and hand and foot, 41.7% and 26.1% (difference, 16.7 percentage points; 95% CI, −6.2 to 36.8; P=0.144). Adverse events occurred among 50% and 42% of participants in the icotrokinra and placebo groups, respectively.

CONCLUSIONS At 16 weeks, significantly higher proportions of participants 12 years of age and over with at least moderate psoriasis involving high-impact sites treated with icotrokinra versus placebo achieved clearance or minimal psoriasis in their skin overall

The author affiliations are listed at the end of the article.

Melinda Gooderham can be contacted at mgooderham@centrefordermatology.com or at SKiN Centre for Dermatology, Department of Dermatology at Queen's University and Probity Medical Research, Peterborough, ON, Canada.

and in the scalp and genital areas, but not in their hands and feet. No safety signals were identified. (Funded by Johnson & Johnson; ClinicalTrials.gov number, NCT06095102.)

Introduction

Plaque psoriasis, a chronic, multisystemic, immune-mediated, inflammatory skin disease, accounts for approximately 90% of psoriasis cases.[1] Psoriasis affecting a large body surface area (BSA) and/or involving high-impact sites (e.g., the scalp, genitals, and hands and feet) can be difficult to treat and significantly diminish health-related quality of life.[2,3] An international Delphi consensus, recently convened by the International Psoriasis Council to recategorize psoriasis severity, emphasized that high-impact site involvement, regardless of BSA affected, should guide decisions on systemic therapy.[3]

Current systemic therapies for plaque psoriasis include injectable biologics targeting tumor necrosis factor alpha (TNFα) or interleukin (IL)-23, IL-12/23, or IL-17, and advanced oral therapies targeting phosphodiesterase 4 (apremilast) and tyrosine kinase 2 (deucravacitinib).[1,4,5] In addition to injection-site reactions,[6] injections are problematic for patients with anxiety and discomfort toward needles.[7,8] Although many patients prefer oral treatments,[9,10] current advanced oral therapies for psoriasis are less efficacious than injectable biologics,[11,12] may have tolerability concerns, and/or are not approved for low-BSA and/or high-impact site psoriasis.[4,5]

Icotrokinra (JNJ-77242113) is a targeted oral peptide that inhibits the IL-23 pathway through a distinct mechanism by selectively blocking the IL-23 receptor (IL-23R), in contrast to current biologic agents that target the IL-23p19 or IL-12/23p40 subunits.[13] In a phase 2b trial in adults with moderate to severe plaque psoriasis (FRONTIER 1), icotrokinra showed higher skin clearance rates at week 16 and similar occurrence of adverse events (AEs) compared with placebo across all doses (daily or twice daily 25–100 mg) through week 16.[14] A long-term extension trial (FRONTIER 2) from weeks 16 to 52 demonstrated sustained skin clearance rates and no safety signals.[15] Icotrokinra 100 mg twice daily demonstrated the highest rate of skin clearance at week 52. Icotrokinra is currently being evaluated in phase 3 trials for moderate to severe plaque psoriasis.

The ICONIC-TOTAL trial, reported here, is a phase 3, double-blind, placebo-controlled trial comparing the efficacy of icotrokinra 200 mg versus placebo to treat adults and adolescents (≥12 years of age) with scalp, genital, and/or hand/foot psoriasis over a 16-week period. Results from the phase 3 ICONIC-LEAD trial of adults and adolescents with moderate to severe plaque psoriasis through week 24 are reported in a companion article.[16]

Methods

TRIAL DESIGN

ICONIC-TOTAL is an ongoing phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, interventional trial, which employed a basket-like design to evaluate the efficacy of icotrokinra in three cohorts of adults and adolescents (≥12 years of age) with scalp, genital, and/or hand/foot psoriasis. The trial, which began on October 12, 2023, is being conducted at 69 sites across Argentina, Canada, Germany, Hungary, Poland, South Korea, Spain, Taiwan, the United Kingdom, and the United States. The trial includes a 5-week screening period; a double-blind, placebo-controlled treatment period (weeks 0–16); an active treatment period (weeks 16–156), during which participants from the placebo group transitioned to icotrokinra; and a 4-week safety follow-up period after the last drug administration (Fig. S1 in the Supplementary Appendix). This report describes ICONIC-TOTAL outcomes through week 16.

Participants were randomly assigned (2:1) to receive either once-daily oral icotrokinra 200 mg or placebo using a computer-generated schedule. Permuted block randomization stratified participants by high-impact site involvement (scalp, genital, hand/foot), geographic region (North and South America, Europe, Asia-Pacific), and BSA category (<10%, ≥10%). The once-daily 200-mg dose was selected based on FRONTIER 1 data[14] and exposure–response modeling[17] demonstrating that this dose would provide clinical response rates comparable with the twice-daily 100-mg dose. Participants were instructed to take the single 200-mg tablet with water, at approximately the same time every day on waking and on an empty stomach, and not to eat for at least 30 minutes after taking the tablet. If participants missed a dose, they were instructed to take it as soon as they remembered. The trial treatment schedules were consistent across all treatment groups, and the labels on the trial treatments were uniform to ensure that both participants and clinicians remained blinded.

TRIAL OVERSIGHT

The trial was conducted according to the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice, and applicable local regulations. The trial protocol was approved by each site's institutional review board or independent ethics committee. Participants provided written informed consent before any trial-related procedures. The trial was sponsored by Johnson & Johnson. Authors M.G., E.L., R.B., C.W.L., E.J.S., J.H.R., A.M.D., T.O., M-C.H., S.L., C.M.C.D., F.N., and R.B.W. designed the trial; and M.G., E.L., R.B., Y.-H.H., C.W.L., M.H., E.J.S., O.W., R.H.G.C., J.H.R., A.M.D., T.O., S.L., C.M.C.D., F.N., and R.B.W. gathered the data. All authors contributed to data analysis and collaborated on writing the manuscript with the assistance of professional medical writers funded by Johnson & Johnson. All authors had full access to the trial data and attest to the accuracy and completeness of the data and fidelity of the trial to the protocol. Confidentiality agreements were instituted between the authors and the sponsor.

PARTICIPANTS

Participants were recruited from dermatology offices, hospitals, and clinical research facilities and screened for eligibility by their dermatology providers. Eligible participants included adults (≥18 years of age) and adolescents (≥12 to <18 years of age) with plaque psoriasis for 26 weeks or more, who were candidates for phototherapy or systemic treatment and had an inadequate response to one or more topical therapies. Participants were eligible if they had a total affected BSA greater than or equal to 1%, an Investigator's Global Assessment (IGA) score greater than or equal to 2 [clear (0), minimal (1), mild (2), moderate (3), or severe (4)[18]]; and at least moderate psoriasis involving one or more high-impact sites defined as a scalp-specific IGA (ss-IGA) score greater than or equal to 3 [absence of disease (0), very mild (1), mild (2), moderate (3), or severe (4)], a static Physician's Global Assessment of Genitalia (sPGA-G) score greater than or equal to 3 [clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5)[19]], and/or PGA of hands and feet (hf-PGA) score ≥3 [clear (0), almost clear (1), mild (2), moderate (3), or severe (4)][20]. Participants were excluded if they had nonplaque psoriasis, palmoplantar pustulosis, or drug-induced psoriasis; had experienced a prior inadequate response or intolerance to at least one other biologic agent targeting IL-23 (other than IL-12/23); or were previously treated with icotrokinra. Eligibility criteria are detailed in Section 5 of the Protocol available at evidence.nejm.org.

Once recruited, participants underwent a baseline evaluation conducted by investigators, which involved a physical examination and assessment of clinical measures, including IGA, ss-IGA, sPGA-G, and hf-PGA (details available in Section 1.3 of the Protocol).

ASSESSMENTS AND END POINTS

Clinical data were collected at baseline, at weeks 2 and 4, and then every 4 weeks through 16 weeks. Investigators conducted in-person assessments to rate the following measures of the participants' psoriasis status: overall skin IGA, ss-IGA, sPGA-G, hf-PGA, and Psoriasis Scalp Severity Index (PSSI) (range, 0–72; higher scores indicate greater severity) scores.[21] During these clinical assessments, participants provided ratings on the following: Scalp Itch Numeric Rating Scale (NRS) (range, 0–10; higher scores indicate worse itch, with clinically meaningful improvement indicated by a decrease of ≥4 points)[22]; Genital Psoriasis Symptoms Scale (GPSS) Genital Itch NRS (range, 0–10; higher scores indicate a worse itch, with clinically meaningful improvement indicated by a decrease of ≥4 points)[23]; Genital Psoriasis Sexual Frequency Questionnaire (GenPs-SFQ)[24] Item 2, which asks how often genital psoriasis symptoms limited the frequency of sexual activity in the previous 7 days [never (0), rarely (1), sometimes (2), often (3), or always (4)]; Psoriasis Symptom and Sign Diary (PSSD) Itch score (range, 0–10; higher scores indicate a worse itch, with clinically meaningful improvement indicated by a decrease of ≥4 points)[25]; and PSSD Symptom score (range, 0–100; higher scores indicate worse symptoms).

All primary and key secondary end points were measured at week 16. The primary end point, an IGA score of 0 or 1, was defined as the proportion of participants achieving an overall skin IGA score of 0 (clear) or 1 (minimal) and an improvement of 2 points or more from baseline. Secondary end points were organized in tiers based on a prespecified sequence for multiplicity adjustment [see Statistical Analysis Plan (SAP) Section 2.1 and pages 2–4 in the Supplementary Appendix]. Tier 1 secondary end points included an ss-IGA score of 0 or 1 (ss-IGA 0/1), an sPGA-G score of 0 or 1 (sPGA-G 0/1), and an hf-PGA score of 0 or 1 (hf-PGA 0/1). The analyses of tier 1 end points included only those participants with at least moderate severity at each high-impact site at baseline (i.e., ss-IGA, sPGA-G, and hf-PGA scores ≥3).

Tier 2 secondary end points included an IGA score of 0 (IGA 0), a PSSD Itch 4-point or greater improvement from baseline among participants with a PSSD Itch score greater than or equal to 4 at baseline, and a PSSD Symptom score of

0 among participants with a PSSD Symptom score greater than 0 at baseline. Other key secondary end points, listed in the fixed sequential order for multiplicity adjustment, included 90% or greater improvement in PSSI score from baseline among participants with ss-IGA score greater than or equal to 3 at baseline, a 4-point or greater improvement in Scalp Itch NRS score from baseline among participants with Scalp Itch NRS score greater than or equal to 4 and ss-IGA score greater than or equal to 3 at baseline, a 4-point or greater improvement in GPSS Genital Itch NRS score from baseline among participants with GPSS Genital Itch NRS score greater than or equal to 4 and sPGA-G score greater than or equal to 3 at baseline, and a GenPs-SFQ Item 2 score of 0 or 1 among participants with a GenPs-SFQ Item 2 score greater than or equal to 2 and a sPGA-G score greater than or equal to 3 at baseline. Section 8.3 of the Protocol details the collection, reporting, and definitions for all safety outcomes, including AEs and serious AEs (SAEs).

STATISTICAL ANALYSES

A planned sample size of 300 participants was estimated to provide greater than 99% power to detect a difference of 56 percentage points for the primary end point — overall IGA 0/1 at week 16 — assuming primary end point response rates of 64% and 8% in the icotrokinra and placebo groups, respectively, at a two-sided α level of 0.05. Approximately 75 evaluable participants within each high-impact site involvement (baseline ss-IGA ≥3, sPGA-G ≥3, and hf-PGA ≥3) subgroup were estimated to provide 90% or greater power to detect a difference of 40 percentage points at a two-sided α-level of 0.05.

The primary efficacy analyses included all randomly assigned participants. The safety analyses included participants who received one or more doses of the trial drug. Primary and key secondary end points were analyzed using the estimand, with nonresponder imputation for participants who discontinued the trial drug due to lack of efficacy or worsening psoriasis, or who initiated a prohibited medication that could impact psoriasis (see Protocol Section 5.2) before week 16. Observed data were used for participants who discontinued treatment for other reasons before week 16. After accounting for these intercurrent events, participants with missing data were considered nonresponders.

Analyses of the primary and key secondary end points employed two-sided (α=0.05) Cochran–Mantel–Haenszel chi-square tests stratified by high-impact site involvement, geographic region, and BSA category, as appropriate. Treatment differences and their corresponding 95% confidence intervals using the Miettinen–Nurminen method were calculated, adjusting for high-impact site involvement, geographic region, and BSA category using Mantel–Haenszel weights, as appropriate. The stratification analysis is detailed on page 5 of the Supplementary Appendix.

Sensitivity analyses using multiple imputation and a tipping point analysis were conducted to assess the impact of missing data for the primary end point (SAP, Section 4.2.3.2). After accounting for intercurrent events, missing data were imputed using multiple imputation by fully conditional specification. In the tipping point analysis, after accounting for intercurrent events, missing IGA 0/1 response statuses were imputed over a range of assumptions of response rates for both treatment groups independently. Both analyses used Mantel–Haenszel weights and Cochran-Mantel–Haenszel chi-square statistics to derive combined overall treatment differences and P values.

A multiplicity adjustment procedure controlled the overall type I error rate at a two-sided 5% level across the primary and key secondary end points, as detailed in Section 2.1 of the SAP and pages 2–4 in the Supplementary Appendix. When the primary end point was significant (P≤0.05), a truncated Bonferroni–Holm procedure was applied to the tier 1 secondary end points. If tier 1 secondary end points of ss-IGA 0/1 and sPGA-G 0/1 were significant at their assigned α-levels, one third of the assigned α-level was passed down to the end points in tier 2. If all tests in tier 2 were significant based on the Bonferroni–Holm procedure, then testing continued to the remaining key end points in a fixed sequential order.

Results

PARTICIPANTS

Between October 12, 2023, and February 20, 2024, 366 individuals were screened for eligibility, among whom 311 were eligible and randomly assigned (icotrokinra, n=208; placebo, n=103) (Fig. S2). Overall, 294 participants [icotrokinra, n=200 (96.2%); placebo, n=94 (91.3%)] completed treatment by week 16. A total of 17 participants [icotrokinra, n=8 (3.8%); placebo, n=9 (8.7%)] discontinued the trial drug before week 16. In the icotrokinra group, discontinuation was due to lack of efficacy (n=3), occurrence of an AE (n=3) (visual blurring or field defect, headache, fungal laryngitis), and withdrawal of consent (n=2). In the placebo group, discontinuation was due to lack of efficacy (n=5), occurrence of an AE (n=3) (psoriatic arthropathy, worsening of psoriasis, coronavirus disease 2019 pneumonia), and withdrawal of consent (n=1).

Baseline demographic characteristics and prior psoriasis treatment history are shown by group in Table 1 and Table S1. A total of 200 (64.3%) participants were male and 243 (78.1%) were White. The mean [± standard deviation (±SD)] age was 44.7 (±14.3) years. Six (1.9%) participants were 12 years of age or older but below 18 years of age. The mean (±SD) disease duration was 16.3 (±12.5) years, 112 (36.0%) participants had affected BSA less than 10%, and 294 (94.5%) had an IGA score greater than or equal to 3 for overall skin involvement. Participants with at least moderate severity of high-impact site psoriasis at baseline were as follows: scalp (ss-IGA score ≥3) [total, n=252 (81.0%); icotrokinra, n=167; placebo, n=85]; genitalia (sPGA-G score ≥3) [total, n=140 (45.0%); icotrokinra, n=98; placebo, n=42], and hands and feet (hf-PGA score ≥3) [total, n=71 (22.8%); icotrokinra, n=48; placebo, n=23]. In terms of representativeness (Table S2), the proportion of White participants in this trial was similar to populations described in psoriasis registries and prior cohort studies,[26-28] whereas the proportion of male

Table 1. Baseline Characteristics of Participants.*

Characteristic	Placebo (N=103)	Icotrokinra (N=208)	Total (N=311)
Age — years, mean±SD	43.5±13.8	45.3±14.6	44.7±14.3
Male sex — no. (%)	63 (61.2)	137 (65.9)	200 (64.3)
Race — no. (%)†			
Asian	20 (19.4)	41 (19.7)	61 (19.6)
Black	0	2 (1.0)	2 (0.6)
White	82 (79.6)	161 (77.4)	243 (78.1)
BMI — mean±SD	29.4±8.1 (n=101)	29.0±6.6 (n=203)	29.2±7.1 (n=304)
Duration of psoriasis — years, mean±SD	15.2±10.5	16.8±13.3	16.3±12.5
Overall IGA score — no. (%)			
3, Moderate plaque psoriasis	73 (70.9)	153 (73.6)	226 (72.7)
4, Severe plaque psoriasis	22 (21.4)	46 (22.1)	68 (21.9)
Percentage affected BSA — mean±SD	14.8±11.7	16.6±13.5	16.0±12.9
<10%	38 (36.9)	74 (35.6)	112 (36.0)
ss-IGA score ≥3 — no. (%)‡	85 (82.5)	167 (80.3)	252 (81.0)
sPGA-G score ≥3 — no. (%)‡	42 (40.8)	98 (47.1)	140 (45.0)
hf-PGA score ≥3 — no. (%)‡	23 (22.3)	48 (23.1)	71 (22.8)
PSSD Symptom score — mean±SD	54.6±26.4 (n=87)	53.2±26.3 (n=191)	53.6±26.3 (n=278)
Previous use of any systemic therapy for psoriasis — no. (%)§	75 (72.8)	151 (72.6)	226 (72.7)
Conventional nonbiologic systemic therapy¶	55 (53.4)	103 (49.5)	158 (50.8)
Phototherapy	32 (31.1)	89 (42.8)	121 (38.9)
Biologic therapy‖	32 (31.1)	71 (34.1)	103 (33.1)
Oral nonbiologic systemic therapy**	7 (6.8)	15 (7.2)	22 (7.1)
1,25-vitamin D_3 and its analogs	6 (5.8)	7 (3.4)	13 (4.2)

* Full baseline characteristics can be found in Table S1. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters); BSA, body surface area [severity range: mild disease (<3%) to severe disease (>10%)]; hf-PGA, Physician's Global Assessment of hands and feet [range: clear (0), almost clear (1), mild (2), moderate (3), or severe (4)]; IGA, Investigator's Global Assessment [range: cleared (0), minimal (1), mild (2), moderate (3), or severe (4)]; SD, standard deviation; sPGA-G, static Physician's Global Assessment of Genitalia [range: clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5)]; PSSD, Psoriasis Symptom and Sign Diary (Symptom score range: 0–100, with higher scores indicating worse symptoms); and ss-IGA, scalp-specific Investigator's Global Assessment [range: absence of disease (0), very mild (1), mild (2), moderate (3), or severe (4)].

† Race was self-reported by participants.

‡ Psoriasis involving high-impact sites was not mutually exclusive.

§ Any prior treatment includes conventional nonbiologic systemic therapies, phototherapy, biologics, oral nonbiologic systemic therapies, and 1,25-vitamin D_3 and its analogs.

¶ Conventional nonbiologic systemic therapy includes acitretin, azathioprine, cyclosporine, fumarate, methotrexate, and psoralen plus ultraviolet A.

‖ Biologic therapy includes adalimumab, alefacept, briakinumab, brodalumab, certolizumab pegol, efalizumab, etanercept, guselkumab, infliximab, ixekizumab, natalizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab.

** Oral nonbiologic systemic therapy includes apremilast, deucravacitinib, and tofacitinib.

individuals was slightly higher, and the mean age lower, due to the inclusion of adolescents.

END POINTS

The primary end point, the proportion of participants achieving overall IGA 0/1, was 56.7% and 5.8% in the icotrokinra and placebo groups, respectively [adjusted difference, 51.1 percentage points; 95% confidence interval (CI), 42.1 to 58.8; P<0.001] (Table 2 and Fig. 1). Sensitivity analyses assessing the impact of missing data assumptions showed consistent results for the primary end point (Fig. S3).

For the tier 1 secondary end points, the proportions of participants in the icotrokinra and placebo groups achieving absent/clear or minimal/almost clear scores in high-impact sites were as follows (Table 2 and Fig. 1): scalp (ss-IGA 0/1), 65.9% and 10.6% (difference, 55.5 percentage points; 95% CI, 44.8 to 64.4; P<0.001); genitalia (sPGA-G 0/1), 76.5% and 21.4% (difference, 55.4 percentage points; 95% CI, 39.1 to 68.0; P<0.001); and hands and feet (hf-PGA), 41.7% and 26.1% (difference, 26 percentage points; 95% CI, −6.2 to 36.8; P=0.14).

The proportions of participants achieving the tier 2 secondary end points in the icotrokinra and placebo groups were as follows (Table 2 and Fig. 2): IGA 0, 25.5% and 1.0% (difference, 24.8 percentage points; 95% CI, 17.4 to 31.5; P<0.001); PSSD Itch 4-point or greater improvement from baseline, 59.5% and 13.5% (difference, 45.2

Table 2. End Points at Week 16.

End Point	Placebo (N=103) No. (%)	Icotrokinra (N=208) No. (%)	Treatment Difference, Adjusted Difference (95% CI); adjusted P value*
Primary end point			
IGA score of 0/1	6/103 (5.8)	118/208 (56.7)	51.1 (42.1 to 58.8); <0.001
Tier 1 secondary end points			
ss-IGA score of 0/1†	9/85 (10.6)	110/167 (65.9)	55.5 (44.8 to 64.4); <0.001
sPGA-G score of 0/1†	9/42 (21.4)	75/98 (76.5)	55.4 (39.1 to 68.0); <0.001
hf-PGA score of 0/1†	6/23 (26.1)	20/48 (41.7)	16.7 (–6.2 to 36.8); 0.14
Tier 2 secondary end points			
IGA score of 0	1/103 (1.0)	53/208 (25.5)	24.8 (17.4 to 31.5); <0.001
PSSD Itch score ≥4-point improvement from baseline‡	10/74 (13.5)	100/168 (59.5)	45.2 (33.4 to 55.3); <0.001
PSSD Symptom score of 0§	3/87 (3.4)	31/191 (16.2)	12.8 (5.5 to 19.4); 0.008
Other key secondary end points			
PSSI score ≥90% improvement from baseline†	5/85 (5.9)	96/167 (57.5)	51.8 (41.7 to 60.3); 0.008
Scalp Itch NRS score ≥4-point improvement from baseline¶	5/58 (8.6)	77/131 (58.8)	50.2 (37.8 to 60.6); 0.008
GPSS Genital Itch NRS score ≥4-point improvement from baseline‖	4/31 (12.9)	44/69 (63.8)	49.8 (31.3 to 64.3); 0.008
GenPs-SFQ Item 2 score of 0/1**	9/25 (36.0)	44/55 (80.0)	43.2 (20.2 to 62.4); 0.008

* P values for key secondary end points were adjusted for multiplicity. Secondary end points were grouped for the multiplicity adjustment as tier 1, tier 2, and other (listed in sequential order for multiplicity adjustment). Details for multiplicity testing are provided on pages 2–4 of the Supplementary Appendix. CI denotes confidence interval; GenPs-SFQ Item 2, Genital Psoriasis Sexual Frequency Questionnaire, which asks how often genital psoriasis symptoms limited sexual activity in the previous 7 days [range: never (0), rarely (1), sometimes (2), often (3), or always (4)]; GPSS Genital Itch NRS, Genital Psoriasis Symptoms Scale in Genital Itch Numeric Rating Scale (range: 0–10; higher scores indicate worse itch, with clinically meaningful improvement indicated by a decrease of ≥4 points from baseline); hf-PGA, Physician's Global Assessment of hands and feet [range: clear (0), almost clear (1), mild (2), moderate (3), or severe (4)]; IGA, Investigator's Global Assessment [range: cleared (0), minimal (1), mild (2), moderate (3), or severe (4)]; PSSD, Psoriasis Symptom and Sign Diary (Symptom range: 0–100; Itch range: 0–10, with higher scores indicating worse symptoms or itch); PSSI, Psoriasis Scalp Severity Index (range: 0–72; higher scores indicate greater severity); Scalp Itch NRS, Scalp Itch Numeric Rating Scale (range: 0–10; higher scores indicate worse itch, with clinically meaningful improvement indicated by a decrease of ≥4 points from baseline); sPGA-G, static Physician's Global Assessment of Genitalia [range: clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5)]; and ss-IGA, scalp-specific Investigator's Global Assessment [range: clear (0), very mild (1), mild (2), moderate (3), or severe (4)].

† For ss-IGA, sPGA-G, and hf-PGA, only participants with baseline scores greater than or equal to 3 were included (ss-IGA: placebo, n=85, icotrokinra, n=167; sPGA-G: placebo, n=42, icotrokinra, n=98; hf-PGA: placebo, n=23, icotrokinra, n=48).

‡ Only participants with a baseline PSSD Itch score greater than or equal to 4 were included (placebo, n=74; icotrokinra, n=168).

§ Only participants with a baseline PSSD Symptom score greater than 0 were included (placebo, n=87; icotrokinra, n=191).

¶ Only participants with baseline scores of Scalp Itch NRS greater than or equal to 4 and ss-IGA greater than or equal to 3 were included (placebo, n=58; icotrokinra, n=131).

‖ Only participants with baseline scores of GPSS Genital Itch NRS greater than or equal to 4 and sPGA-G greater than or equal to 3 were included (placebo, n=31; icotrokinra, n=69).

** Only participants with baseline scores of GenPs-SFQ Item 2 greater than or equal to 2 and sPGA-G greater than or equal to 3 were included (placebo, n=25; icotrokinra, n=55).

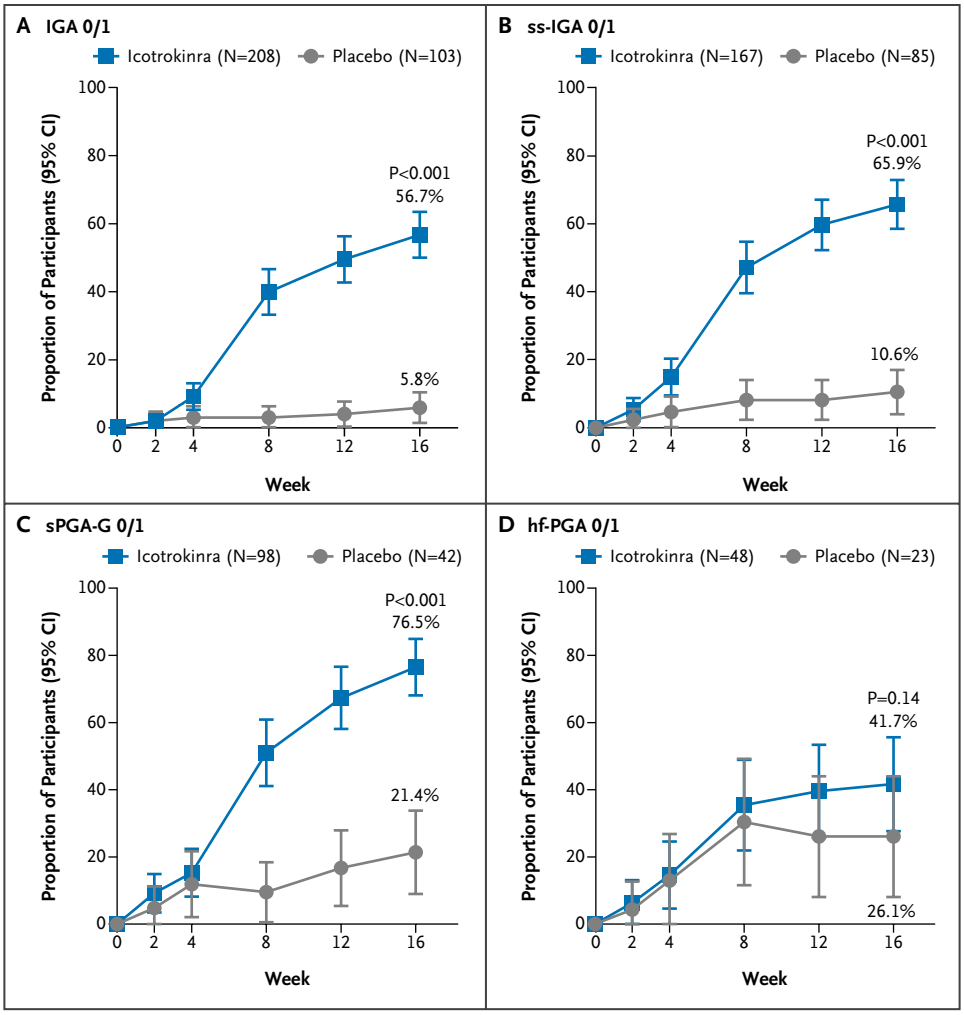

Figure 1. Primary and Tier 1 Secondary End Points at Week 16 and Each Assessment up to Week 16.

The end points were assessed in person by investigators at baseline, and at weeks 2, 4, 8, 12, and 16. P values compare 16-week end points between the icotrokinra and placebo groups. P values for secondary end points were adjusted for multiplicity. Tier 1 refers to the set of secondary end points prespecified in the first level of multiplicity adjustments. Details for multiplicity adjustments are provided on pages 2–4 of the Supplementary Appendix. Vertical lines denote the width of the 95% confidence intervals. Panel A shows the IGA 0/1 primary end point. Panel B shows the ss-IGA 0/1 tier 1 secondary end point. Panel C shows the sPGA-G 0/1 tier 1 secondary end point. Panel D shows the hf-PGA 0/1 tier 1 secondary end point. For ss-IGA, sPGA-G, and hf-PGA, only participants with baseline scores greater than or equal to 3 for these end points were included. CI denotes confidence interval; hf-PGA, Physician's Global Assessment of hands and feet [range: clear (0), almost clear (1), mild (2), moderate (3), or severe (4)]; IGA, Investigator's Global Assessment [range: cleared (0), minimal (1), mild (2), moderate (3), or severe (4)]; sPGA-G, static Physician's Global Assessment of Genitalia [range: clear (0), minimal (1), mild (2), moderate (3), severe (4), or very severe (5)]; ss-IGA, scalp-specific Investigator's Global Assessment [range: absence of disease (0), very mild (1), mild (2), moderate (3), or severe (4)]; and 0/1, a score of 0 or 1 on the respective scale.

percentage points; 95% CI, 33.4 to 55.3; P<0.001); and PSSD Symptom score of 0, 16.2% and 3.4% (difference, 12.8 percentage points; 95% CI, 5.5 to 19.4; P=0.008).

The proportions of participants achieving the other key secondary end points in the icotrokinra and placebo groups, listed in the prespecified sequential order for multiplicity adjustment, were as follows (Table 2 and Fig. S4): 90% or greater improvement in PSSI score, 57.5% and 5.9% (difference, 51.8 percentage points; 95% CI, 41.7 to 60.3; P=0.008); 4-point or greater improvement in Scalp Itch NRS score, 58.8% and 8.6% (difference, 50.2 percentage points; 95% CI, 37.8 to 60.6; P=0.008); 4-point or greater improvement in GPSS Genital Itch NRS score, 63.8% and

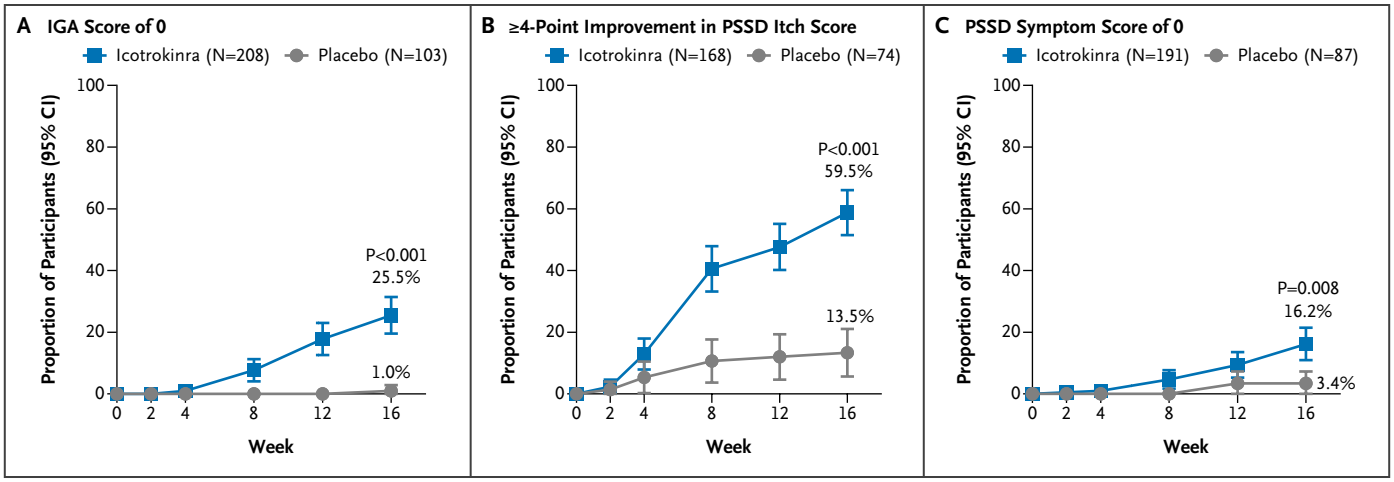

Figure 2. Tier 2 Secondary End Points at Week 16 and Each Assessment up to Week 16.

End points were assessed in person by investigators (IGA 0) or based on participant reports (PSSD) ascertained at baseline, and at weeks 2, 4, 8, 12, and 16. P values compare 16-week end points between the icotrokinra and placebo groups and were adjusted for multiplicity. Tier 2 refers to the set of secondary end points prespecified for the second level of multiplicity adjustments. Details for multiplicity adjustment are provided on pages 2–4 of the Supplementary Appendix. Vertical lines denote the width of the 95% confidence intervals. Panel A shows the IGA score of 0 end point. Panel B shows the 4-point or greater improvement in PSSD Itch score end point. Panel C shows the PSSD Symptom score of 0 end point. For PSSD Itch, only participants with a baseline score greater than or equal to 4 were included. For PSSD Symptom, only participants with a baseline score greater than 0 were included. CI denotes confidence interval; IGA, Investigator's Global Assessment [range: cleared (0), minimal (1), mild (2), moderate (3), severe (4)]; and PSSD, Psoriasis Symptom and Sign Diary (Symptom score range: 0–100; Itch score range: 0–10, with higher scores indicating worse symptoms of itch, and clinically meaningful improvement indicated by a decrease of ≥4 points).

12.9% (difference, 49.8 percentage points; 95% CI, 31.3 to 64.3; P=0.008); and a GenPs-SFQ Item 2 score of 0 or 1, 80.0% and 36.0% (difference, 43.2 percentage points; 95% CI, 20.2 to 62.4; P=0.008).

SAFETY FINDINGS

Detailed safety outcomes are presented in Table S3. Through week 16, treatment-emergent AEs occurred in 50.0% and 41.7% of participants in the icotrokinra and placebo groups, respectively (Table 3). The most common AEs were nasopharyngitis (icotrokinra, 12.5%; placebo, 10.7%) and upper respiratory tract infection (icotrokinra, 4.3%; placebo, 4.9%). SAEs occurred in 0.5% of icotrokinra-treated and 1.9% of placebo-treated participants. The proportion of participants experiencing other AEs in the icotrokinra and placebo groups, respectively, included gastrointestinal AEs, 7.2% and 7.8%; infections, 28.4% and 21.4%; and serious infections, 0% and 1.0%. As detailed on page 6 of the Supplementary Appendix, a melanoma was reported in a participant in the icotrokinra group who had a prior history of melanoma. No deaths were reported.

Twenty-one participants with latent tuberculosis infection (LTBI) were identified at baseline, among whom 11 (icotrokinra, n=6; placebo, n=5) did not receive treatment for LTBI, 3 (icotrokinra, n=3; placebo, n=0) received concomitant treatment for LTBI based on the investigator's discretion, and 7 (icotrokinra, n=6; placebo, n=1) were previously treated for LTBI. No treatment-emergent active or latent tuberculosis was reported during the trial.

Discussion

ICONIC-TOTAL evaluated the efficacy of icotrokinra, a targeted oral peptide with a novel mechanism of action, among participants 12 years of age and over with 1% or greater BSA affected and at least moderate scalp, genital, and/or hand/foot plaque psoriasis. At 16 weeks, a significantly higher proportion of participants treated with icotrokinra versus placebo achieved absence/clearance or minimal/almost clear psoriasis in their skin overall and scalp and genital areas, but not in their hands and feet. No safety signals were identified.

High-impact site psoriasis is often recalcitrant to treatment.[2,3] The results of this trial provide evidence of the potential utility of blocking the IL-23R with icotrokinra for

Table 3. Safety Outcomes through Week 16.*

Adverse Event	Placebo (N=103)	Icotrokinra (N=208)
Duration of follow-up — weeks, mean±SD	15.7±1.9	16.0±1.8
Any AE — no. (%)	43 (41.7)	104 (50.0)
Most common AEs (≥5%) — no. (%)		
Nasopharyngitis	11 (10.7)	26 (12.5)
Upper respiratory tract infection	5 (4.9)	9 (4.3)
Headache	6 (5.8)	6 (2.9)
AE leading to discontinuation of trial drug† — no. (%)	3 (2.9)	4 (1.9)
SAE‡ — no. (%)	2 (1.9)	1 (0.5)
Gastrointestinal AEs — no. (%)	8 (7.8)	15 (7.2)
Infections — no. (%)	22 (21.4)	59 (28.4)
Serious infection	1 (1.0)	0
Malignancy§	0	1 (0.5)
Active tuberculosis	0	0

* Detailed safety outcomes are presented in Table S3. AE, adverse event; SAE, serious adverse event; and SD, standard deviation.
† AEs leading to discontinuation of trial drug included coronavirus disease 2019 (Covid-19) pneumonia (n=1), psoriatic arthropathy (n=1), and psoriasis (n=1) in the placebo group; and vision blurring or field defect (n=1), fungal laryngitis (n=1), malignant melanoma in situ* (n=1), and headache (n=1) in the icotrokinra group.
‡ SAEs included acute respiratory failure, Covid-19 pneumonia, and sepsis in the same participant (n=1), and sciatica (n=1) in the placebo group; and hepatitis (n=1) in the icotrokinra group.
§ Malignant melanoma in situ in a participant with a history of melanoma (page 6 of the Supplementary Appendix).

treating high-impact site plaque psoriasis and corroborate findings from the ongoing ICONIC-LEAD and ICONIC-ADVANCE trials and the completed FRONTIER trials in participants with moderate to severe plaque psoriasis.[14-16,29] The lack of safety signals observed herein through week 16 and in the ICONIC-LEAD and ICONIC-ADVANCE trials through week 24 are also consistent with the FRONTIER trials through 1 year.[14-16,29] Taken together, to date, the evidence evaluating the efficacy and safety of icotrokinra is consistent across various populations with plaque psoriasis, including adults, adolescents, and those with low BSA and high-impact site involvement.

Recent trials have reported on scalp, genital, and palmoplantar plaque psoriasis management using apremilast[30-34] and on scalp psoriasis using deucravacitinib,[35-37] yet these oral treatments showed modest efficacy in treating psoriasis relative to biologics.[11,12] IL-23–targeting biologics are effective in treating scalp and genital psoriasis,[38-41] supporting IL-23 pathway inhibition as an effective strategy for high-impact site psoriasis. In this trial, clearance rates for overall skin, scalp, and genital psoriasis with icotrokinra were within the range of those observed with approved IL-23– and IL-17–targeting biologics.[38-43] However, interpretations are restricted by differences in trial populations, placebo response rates, and statistical methodologies. Hand/foot psoriasis clearance in the icotrokinra versus placebo group was not statistically significant, which may be attributed to the fact that 35% of participants in the icotrokinra group versus 17% in the placebo group had a baseline hf-PGA score of 4, the small sample size in this subgroup, and a higher-than-expected placebo response rate. In addition, different biological pathways play a predominant role in hand/foot psoriasis, which may impact the response to biologics inhibiting TNF-α, IL-23, and IL-17 relative to other high-impact sites.[20,44-47]

Trial results are constrained by the low number of adolescents and the lack of an active control comparator. The placebo was chosen for the comparative group to establish the efficacy and safety profile of icotrokinra, ultimately aiding informed decision-making regarding approval. However, ongoing comparison investigations of icotrokinra versus available therapies, such as deucravacitinib (ICONIC-ADVANCE 1 and 2,[29] NCT06220604, NCT06143878) and ustekinumab (NCT06934226), are being conducted in participants with plaque psoriasis, including those with high-impact site involvement. We employed nonresponder imputation for missing data, which might underestimate the standard error and affect the estimated treatment differences. However, the number of missing data was low in this trial and the sensitivity analyses were consistent with the primary end point analysis. Although findings are also

limited by the relatively short treatment duration, long-term maintenance data are being collected over the course of 3 years, which is particularly relevant given the chronicity of psoriasis. ICONIC-TOTAL also demonstrates the usefulness of basket-like trial designs to efficiently investigate treatments among cohorts of participants with psoriasis affecting high-impact sites.

In conclusion, among adults and adolescents with affected BSA greater than or equal to 1% and at least moderate psoriasis affecting high-impact areas, icotrokinra, a targeted oral peptide that blocks the IL-23R, demonstrated significantly higher rates of overall skin, scalp, and genital psoriasis clearance at week 16, but findings were not statistically significant for hand/foot psoriasis. This trial also supports the safety of icotrokinra over 16 weeks, with future work needed to address longer-term safety outcomes.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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Author Affiliations

[1] SKiN Centre for Dermatology, Department of Medicine at Queen's University and Probity Medical Research, Peterborough, ON, Canada

[2] Austin Institute for Clinical Research, Sanova Dermatology, Austin, TX, USA

[3] Innovaderm Research, Montreal, QC, Canada

[4] Department of Dermatology, Chang Gung Memorial Hospital and College of Medicine, Chang Gung University, Taoyuan City, Taiwan

[5] Department of Medicine, University of Toronto, Toronto, ON, Canada

[6] The Lynde Institute for Dermatology and Lynderm Research Inc., Markham, ON, Canada

[7] Dermatology Practice Dr. Matthias Hoffmann, Witten, Germany

[8] Frontier Dermatology, Mill Creek, WA, USA

[9] Rosenpark Research, Darmstadt, Germany

[10] Private Family Medicine Center, Autonomous City of Buenos Aires, Argentina

[11] Johnson & Johnson, Spring House, PA, USA

[12] Dermatology Centre, Northern Care Alliance NHS Foundation Trust and Division of Musculoskeletal and Dermatological Sciences, Manchester NIHR Biomedical Research Centre, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK

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