ORIGINAL ARTICLE

Oral Icotrokinra for Plaque Psoriasis in Adults and Adolescents

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ABSTRACT

BACKGROUND

Icotrokinra, a targeted oral peptide that selectively binds the interleukin-23 receptor, is under investigation for the treatment of plaque psoriasis.

METHODS

We conducted a phase 3, double-blind, randomized, placebo-controlled trial involving adults and adolescents (≥12 years of age) with moderate-to-severe plaque psoriasis, as defined by all the following: a total body-surface area of psoriasis involvement of at least 10%, a Psoriasis Area and Severity Index (PASI) score of at least 12 (range, 0 to 72, with higher scores indicating a greater extent or severity of psoriasis), and an Investigator's Global Assessment (IGA) score of at least 3 (range, 0 [clear skin] to 4 [severe disease]). Participants were assigned in a 2:1 ratio to receive icotrokinra at a dose of 200 mg once daily through week 24 or placebo through week 16 followed by transition to icotrokinra. The coprimary end points were an IGA 0/1 response (IGA score of 0 or 1 with ≥2-point reduction from baseline) and a PASI 90 response (≥90% reduction from baseline in the PASI score) at week 16.

RESULTS

A total of 684 participants underwent randomization (456 to the icotrokinra group and 228 to the placebo group). At week 16, a total of 65% of the participants receiving icotrokinra and 8% of those receiving placebo had an IGA 0/1 response, and 50% and 4%, respectively, had a PASI 90 response (P<0.001 for both comparisons). Complete clearance of skin at week 16 was significantly more likely with icotrokinra than with placebo (IGA score of 0, 33% vs. 1%; PASI 100 response [100% reduction from baseline in the PASI score], 27% vs. <1%; P<0.001 for both comparisons). The percentage of participants with at least one adverse event through week 16 was 49% in each group; the most common adverse events in each group were nasopharyngitis and upper respiratory tract infection. The exposure-adjusted incidence of adverse events was consistent through week 24.

CONCLUSIONS

Selective blockade of the interleukin-23 receptor with the targeted oral peptide icotrokinra resulted in a significantly higher incidence of skin clearance at week 16 than placebo among adults and adolescents with moderate-to-severe plaque psoriasis. Longer-term data will provide a more complete understanding of the benefit–risk profile of icotrokinra. (Funded by Johnson & Johnson; ICONIC-LEAD ClinicalTrials.gov number, NCT06095115.)

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CME

Psoriasis, a chronic, immune-mediated inflammatory skin disease, affects approximately 125 million persons worldwide.[1] Patients with moderate-to-severe plaque psoriasis can be treated with systemic therapy, including biologic agents such as inhibitors of tumor necrosis factor α and interleukin-12, -17, and -23.[1] These biologic therapies are highly effective but only available by injection, which can be problematic for persons with anxiety and discomfort with needles,[2] for adolescents and children, and for those who prefer oral treatments over injections.[3,4] Although advanced oral therapies, such as apremilast and deucravacitinib, are available, these medications show less efficacy than biologics[5-8] and are associated with adverse events.[9,10] Of the oral agents, only apremilast is currently approved by the Food and Drug Administration (FDA) and European Medicines Agency for treating patients 6 to younger than 18 years of age.[9-11]

Icotrokinra (JNJ-77242113) is a targeted oral peptide that selectively blocks the interleukin-23 receptor. This mechanism of inhibiting the interleukin-23 pathway differs from the mechanism of biologics that target the p19 subunit of interleukin-23 or the p40 subunit of interleukin-12 and interleukin-23.[12] Blocking the interleukin-23 pathway is a validated approach for treating moderate-to-severe plaque psoriasis[13-16] and other immune-mediated inflammatory diseases.[17] In a phase 2b trial involving adults with moderate-to-severe plaque psoriasis (FRONTIER 1), treatment with icotrokinra resulted in a higher percentage of participants with skin clearance at week 16 than placebo, and the incidence of adverse events through week 16 across all doses (25 to 100 mg once or twice daily) was similar to that with placebo.[18] A long-term extension trial (FRONTIER 2) showed sustained skin clearance and no safety signals through 52 weeks of icotrokinra treatment.[19] Icotrokinra at a dose of 100 mg twice daily showed the highest likelihood of responses, with more than 40% of participants having completely clear skin at week 52.[19]

Icotrokinra is being evaluated in phase 3 trials for moderate-to-severe plaque psoriasis (ICONIC-LEAD) and for psoriasis involving difficult-to-treat sites (scalp, genitals, hands, and feet; ICONIC-TOTAL). In this report, we describe results from the ICONIC-LEAD trial through week 24 in adults and adolescents (≥12 years of age) with moderate-to-severe plaque psoriasis. (Results from the ICONIC-TOTAL trial are reported in a companion article in *NEJM Evidence*.[20])

METHODS

PARTICIPANTS

Eligible adults (≥18 years of age) and adolescents (12 to <18 years of age) had moderate-to-severe plaque psoriasis (as defined by a total body-surface area of psoriasis involvement of ≥10%, a Psoriasis Area and Severity Index [PASI] score of ≥12, and an Investigator's Global Assessment [IGA] score of ≥3), had received a diagnosis of plaque psoriasis at least 26 weeks before screening, and were candidates for phototherapy or other systemic treatment for plaque psoriasis. IGA scores range from 0 (clear skin) to 4 (severe disease). PASI scores range from 0 to 72, with higher scores indicating a greater extent or severity of psoriasis. Persons with nonplaque psoriasis, drug-induced psoriasis, previous treatment failure with or adverse events related to at least one biologic targeting interleukin-23, or previous receipt of icotrokinra were excluded (previous treatment failure with a biologic targeting both interleukin-12 and interleukin-23 was allowed). Full eligibility criteria are described in the protocol, available with the full text of this article at NEJM.org.

A Quick Take is available at NEJM.org

TRIAL DESIGN

ICONIC-LEAD is an ongoing phase 3, multicenter, double-blind, randomized, placebo-controlled, interventional trial being conducted across 138 sites in Argentina, Australia, Canada, China, Germany, Hungary, Italy, Japan, Poland, South Korea, Spain, Taiwan, Turkey, the United Kingdom, and the United States. The trial includes a 5-week screening period; a double-blind, placebo-controlled treatment period (weeks 0 through 16); an active-treatment period, during which participants receiving placebo transitioned to icotrokinra (after week 16 and continuing through week 24); a randomized withdrawal and retreatment period (after weeks 24 and continuing through week 52) for adults with a treatment response; an open-label active-treatment period (after weeks 52 and continuing through week 156); and a 4-week safety follow-up after the last dose of icotrokinra (Fig. S1 in the Supplementary Appendix, available at NEJM.org). This report describes results through week 24.

Participants were randomly assigned (in a 2:1 ratio) to receive once-daily icotrokinra (200 mg) for 24 weeks or placebo for 16 weeks followed by transition to icotrokinra (placebo to icotrokinra). Randomization, conducted with the use of a computer-generated schedule, was stratified according to age group (12 to <18 years or ≥18 years), baseline weight category (adults only; ≤90 kg or >90 kg), and geographic region (North and South America, Europe, or Asia–Pacific). The 200-mg once-daily dose was selected on the basis of FRONTIER 1 data[18] and exposure–response modeling[21] showing that this dose would produce clinical responses similar to those with the 100-mg twice-daily dose. Participants were instructed to take a single tablet with water at approximately the same time every day on waking, with no food intake until at least 30 minutes after. If participants missed a dose, they were instructed to take it on remembering. For adolescents with difficulty swallowing tablets, icotrokinra or placebo could be suspended in a glass of water and fully taken within 15 minutes.

TRIAL OVERSIGHT

The trial was conducted according to the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonisation, and applicable local regulations. The trial protocol was approved by the institutional review board or independent ethics committee at each trial site. Participants provided written informed consent before participating in any trial procedures. The trial was sponsored by Johnson & Johnson. Details regarding author contributions are provided in the Supplementary Appendix. All the authors collaborated on writing the manuscript with the assistance of professional medical writers funded by Johnson & Johnson. All the authors had full access to the trial data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Confidentiality agreements were established between the authors and the sponsor.

END POINTS

The coprimary end points were an IGA 0/1 response (IGA score[22] of 0 [clear skin] or 1 [minimal disease] with ≥2-point reduction from baseline) and a PASI 90 response (≥90% reduction from baseline in the PASI score[23]) at week 16. Key secondary end points at week 16 included a PASI 75 response (≥75% reduction in the PASI score), a PASI 100 response (100% reduction in the PASI score), an IGA score of 0, and a scalp-specific IGA 0/1 response (scalp-specific IGA score of 0 or 1 [range, 0 {absence of disease} to 4 {severe disease}] with ≥2-point reduction from baseline; assessed among participants with a baseline score of ≥2). Participant-reported outcomes that were included as key secondary end points at week 16 were a Psoriasis Symptoms and Signs Diary (PSSD) symptom score[24] of 0 (range, 0 to 100, with higher scores indicating a greater severity of symptoms; assessed among participants with a baseline score of >0) and a clinically meaningful improvement (≥4-point reduction from baseline) in the PSSD itch score (range, 0 to 10, with higher scores indicating a greater severity of itching; assessed among participants with a baseline score of ≥4). In addition, a PASI 90 response at week 8, a PSSD symptom score of 0 at week 8, a PASI 75 response at week 4, and a clinically meaningful improvement in the PSSD itch score at week 4 were key secondary end points. A Dermatology Life Quality Index (DLQI) score[25] of 0 or 1 (range, 0 to 30, with higher scores indicating greater impairment in quality of life due to skin conditions) at week 16 among adult participants with a baseline score of more than 1 was an additional secondary end point. Safety assessments included documentation of adverse events, serious adverse events, and clinical laboratory assessments.

STATISTICAL ANALYSIS

We estimated that a sample of 600 evaluable participants would provide the trial with at least 99% power to detect differences between icotrokinra and placebo for the coprimary end points, assuming an incidence of IGA 0/1 and PASI 90 responses at week 16 of 64% and 59%, respectively, in the icotrokinra group and an incidence of 8% and 5%, respectively, in the placebo group (at a two-sided alpha level of 0.05).

The primary efficacy analyses included all the participants who underwent randomization, and the safety analyses included all the participants who received at least one dose of icotrokinra or placebo. Coprimary and key secondary end points were analyzed with the use of the estimand, with imputation of nonresponse for participants who discontinued the trial regimen owing to lack of efficacy or an adverse event involving worsening

psoriasis or who initiated a prohibited medication that could affect psoriasis before week 16. Observed data were used for participants who discontinued the trial regimen for other reasons before week 16. After we accounted for these intercurrent events, participants with missing data were considered not to have had a response. Analyses of the coprimary and key secondary end points used a two-sided (alpha level, 0.05) Cochran–Mantel–Haenszel chi-square test stratified according to age group, baseline weight category (adults only), and geographic region, as appropriate. Between-group differences and their corresponding 95% confidence intervals (determined with the Miettinen–Nurminen method) were calculated with adjustment for age group, baseline weight category (adults only), and geographic region with the use of Mantel–Haenszel weights, as appropriate. Fisher's exact test was used for the end point of a PSSD symptom score of 0 at week 8.

A multiplicity-adjustment procedure controlled the overall type I error rate at a two-sided level of 0.05 across the coprimary and key secondary end points assessed through week 16. Beginning with the test of superiority of icotrokinra to placebo for the coprimary end points, the key secondary end points would be tested only if the results for both coprimary end points were significant ($P \leq 0.05$). For key secondary end points, statistical significance was claimed if the multiplicity-adjusted P value was 0.05 or less. Details of multiplicity testing are provided in the Methods section in the Supplementary Appendix.

RESULTS

PARTICIPANTS

Between October 12, 2023, and April 4, 2024, a total of 837 persons were assessed for eligibility and 684 (82%) underwent randomization (456 to the icotrokinra group and 228 to the placebo group) (Fig. S2). Of the participants who underwent randomization, 66 (10%) were adolescents (44 in the icotrokinra group and 22 in the placebo group). Overall, 651 participants (437 [96%] in the icotrokinra group and 214 [94%] in the placebo group) completed the trial regimen through week 16. Among the 33 participants (19 [4%] in the icotrokinra group and 14 [7%] in the placebo group) who discontinued the trial regimen before week 16, the most common reasons were withdrawal by the participant in the icotrokinra group (8 participants [2%]) and lack of efficacy in the placebo group (8 participants [4%]). At week 16, a total of 213 participants (93%) transitioned from placebo to icotrokinra. After week 16 and continuing through week 24, a total of 2 participants (<1%) discontinued the trial regimen (1 in the icotrokinra group and 1 in the placebo-to-icotrokinra group), both owing to an adverse event involving worsening psoriasis.

Most participants were male (65%) and White (72%). The demographic and clinical characteristics (including previous psoriasis treatment) of the participants at baseline were similar in the icotrokinara and placebo groups, both in the overall population and in the adolescent subgroup (Table 1 and Tables S1 and S2). The representativeness of the trial population is described in Table S3.

CLINICAL RESPONSES

With respect to the coprimary end points, an IGA 0/1 response at week 16 occurred in 65% of the participants receiving icotrokinra and in 8% of those receiving placebo (difference, 56.4 percentage points [95% confidence interval {CI}, 50.4 to 61.7]; P<0.001), and a PASI 90 response at week 16 occurred in 50% and 4%, respectively (difference, 45.1 percentage points [95% CI, 39.5 to 50.4]; P<0.001) (Table 2 and Fig. 1). Sensitivity analyses that assessed the effect of missing-data assumptions showed results consistent with those of the primary analyses (Fig. S3).

At week 16, significantly higher percentages of participants receiving icotrokinra than those receiving placebo had a PASI 75 response (69% vs. 11%), a PASI 100 response (27% vs. <1%), and an IGA score of 0 (33% vs. 1%) (P<0.001 for all comparisons) (Fig. 1). In addition, significantly higher percentages of participants receiving icotrokinra than those receiving placebo had a PASI 75 response at week 4 (15% vs. 2%; P=0.002) and a PASI 90 response at week 8 (21% vs. 1%; P<0.001). Among participants with a scalp-specific IGA score of 2 or more at baseline, a significantly higher percentage of participants receiving icotrokinra than those receiving placebo had a scalp-specific IGA 0/1 response at week 16 (72% vs. 15%; P<0.001) (Fig. 2). Across assessments, separation of response curves between participants receiving icotrokinra and those receiving placebo was observed as early as week 4

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Icotrokinra (N=456)	Placebo (N=228)	Total (N=684)
Age — yr	42.4±16.3	43.2±16.6	42.6±16.4
Male sex — no. (%)	291 (64)	156 (68)	447 (65)
Race or ethnic group — no. (%)†			
American Indian, Alaska Native, Native Hawaiian, or Pacific Islander	2 (<1)	1 (<1)	3 (<1)
Asian	110 (24)	57 (25)	167 (24)
Black	6 (1)	2 (<1)	8 (1)
White	329 (72)	165 (72)	494 (72)
Body-mass index‡	29.2±6.9	29.3±7.0	29.3±7.0
Duration of psoriasis — yr	17.3±13.9	16.6±12.7	17.1±13.5
PASI total score§	19.4±7.1	20.8±8.1	19.9±7.5
IGA score — no. (%)¶			
3, Moderate plaque psoriasis	341 (75)	173 (76)	514 (75)
4, Severe plaque psoriasis	115 (25)	55 (24)	170 (25)
Percentage of affected body-surface area‖	24.6±14.3	27.1±16.2	25.5±15.0
Scalp-specific IGA score — no./total no. (%)**			
3, Moderate scalp psoriasis	268/451 (59)	116/227 (51)	384/678 (57)
4, Severe scalp psoriasis	76/451 (17)	49/227 (22)	125/678 (18)
PSSD symptom score††	50.1±25.8	49.4±25.4	49.9±25.6
PSSD itch score	6.2±2.5	6.3±2.4	6.2±2.4
DLQI score‡‡	11.4±6.7	11.0±6.4	11.3±6.6
Previous use of systemic therapy for psoriasis — no. (%)§§	327 (72)	163 (71)	490 (72)
Conventional nonbiologic systemic therapy¶¶	217 (48)	109 (48)	326 (48)
Biologic therapy‖‖	148 (32)	85 (37)	233 (34)
Phototherapy	136 (30)	67 (29)	203 (30)
Nonconventional nonbiologic systemic therapy***	37 (8)	17 (7)	54 (8)

* Plus–minus values are means ±SD.
† Race and ethnic group were reported by the participant.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were available for 455 participants in the icotrokinra group and 227 participants in the placebo group.
§ Scores on the Psoriasis Area and Severity Index (PASI) range from 0 to 72, with higher scores indicating a greater extent or severity of psoriasis.
¶ Scores on the Investigator's Global Assessment (IGA) range from 0 (clear skin) to 4 (severe disease).
‖ The percentage of affected body-surface area was used to assess the involvement of psoriasis and classify the severity, ranging from less than 3% (mild disease) to greater than 10% (severe disease).
** Scalp-specific IGA scores range from 0 (absence of disease) to 4 (severe disease).
†† Psoriasis Symptoms and Signs Diary (PSSD) symptom scores range from 0 to 100, with higher scores indicating a greater severity of symptoms. PSSD itch scores range from 0 to 10, with higher scores indicating a greater severity of itching. Data were available for 410 participants in the icotrokinra group and 209 participants in the placebo group.
‡‡ Scores on the Dermatology Life Quality Index (DLQI) range from 0 to 30, with higher scores indicating greater impairment in quality of life due to skin conditions. DLQI scores were assessed only in adult participants. Data were available for 412 participants in the icotrokinra group and 206 participants in the placebo group.
§§ Systemic therapies include biologic therapy, conventional nonbiologic systemic therapies, nonconventional (oral) nonbiologic systemic therapies, phototherapy, and 1,25-dihydoxyvitamin D and analogues.
¶¶ This category includes acitretin, azathioprine, cyclosporine, fumarate, methotrexate, and psoralen plus ultraviolet A.
‖‖ This category includes adalimumab, alefacept, briakinumab, brodalumab, certolizumab pegol, efalizumab, etanercept, guselkumab, infliximab, ixekizumab, natalizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab.
*** This category includes the oral agents apremilast, deucravacitinib, and tofacitinib.

Table 2. Coprimary and Key Secondary End Points through Week 16.*

End Point	Icotrokinra (N=456)	Placebo (N=228)	Difference (95% CI)	Adjusted P Value†
			percentage points	
Coprimary end points				
IGA 0/1 response at wk 16 — no. (%)	295 (65)	19 (8)	56.4 (50.4–61.7)	<0.001
PASI 90 response at wk 16 — no. (%)	226 (50)	10 (4)	45.1 (39.5–50.4)	<0.001
Key secondary end points				
PASI 75 response at wk 16 — no. (%)	315 (69)	25 (11)	58.1 (51.9–63.6)	<0.001
PASI 100 response at wk 16 — no. (%)	123 (27)	1 (<1)	26.5 (22.4–30.8)	<0.001
IGA score of 0 at wk 16 — no. (%)	152 (33)	3 (1)	31.9 (27.2–36.6)	<0.001
Scalp-specific IGA 0/1 response at wk 16 — no./total no. (%)‡	293/405 (72)	30/200 (15)	57.0 (49.9–63.1)	<0.001
PSSD symptom score of 0 at wk 16 — no./total no. (%)§	82/408 (20)	2/208 (<1)	19.2 (15.0–23.6)	<0.001
Clinically meaningful improvement in PSSD itch score at wk 16 — no./total no. (%)¶	203/350 (58)	23/176 (13)	45.2 (37.5–52.0)	<0.001
PASI 90 response at wk 8 — no. (%)	98 (21)	3 (1)	20.1 (15.9–24.5)	<0.001
PSSD symptom score of 0 at wk 8 — no./total no. (%)§	29/408 (7)	3/208 (1)	5.7 (2.0–8.9)	0.002
PASI 75 response at wk 4 — no. (%)	68 (15)	5 (2)	12.7 (8.8–16.6)	0.002
Clinically meaningful improvement in PSSD itch score at wk 4 — no./total no. (%)¶	67/350 (19)	9/176 (5)	14.1 (8.6–19.3)	0.002

* IGA 0/1 response refers to an IGA score of 0 (clear skin) or 1 (minimal disease) with a reduction from baseline of at least 2 points. Scalp-specific IGA 0/1 response refers to a scalp-specific IGA score of 0 (absence of disease) or 1 (very mild disease) with a reduction from baseline of at least 2 points. PASI 75 response, PASI 90 response, and PASI 100 response refer to reductions from baseline of at least 75%, 90%, and 100%, respectively, in the PASI score. Clinically meaningful improvement in the PSSD itch score refers to a reduction from baseline of at least 4 points.

† P values for key secondary end points were adjusted for multiplicity. Details of multiplicity testing are provided in the Methods section in the Supplementary Appendix.

‡ This end point was assessed in participants with a baseline scalp-specific IGA score of 2 or more.

§ This end point was assessed in participants with a baseline PSSD symptom score of more than 0.

¶ This end point was assessed in participants with a baseline PSSD itch score of 4 or more.

or 8. Among participants receiving icotrokinra, the mean (±SD) percentage of body-surface affected by psoriasis decreased from 24.6±14.3 at baseline to 6.1±8.8 at week 16, whereas among participants receiving placebo, it remained consistent (27.1±16.2 and 22.6±15.6, respectively). Through week 24, the incidence of response among participants assigned to receive icotrokinra increased across assessments, including an IGA 0/1 response (74%), a PASI 90 response (65%), an IGA score of 0 (46%), and a PASI 100 response (40%).

In the adolescent subgroup, an IGA 0/1 response at week 16 occurred in 84% of the participants receiving icotrokinra and in 27% of those receiving placebo (difference, 56.2 percentage points; 95% CI, 33.2 to 74.1), and a PASI 90 response at week 16 occurred in 70% and 14%, respectively (difference, 56.3 percentage points; 95% CI, 32.5 to 73.0) (Table S4). The percentage of participants who had a response to icotrokinra continued to increase through week 24 of treatment (IGA 0/1 response, 86%; PASI 90 response, 89%).

PARTICIPANT-REPORTED OUTCOMES

A significantly higher percentage of participants receiving icotrokinra than those receiving placebo had a PSSD symptom score of 0 at week 8 (7% vs. 1%; P=0.002), with amplification of treatment effect through week 16 (20% vs. 1%; P<0.001) (mean change from baseline in the PSSD symptom score, −33.8±25.1 vs. −5.2±24.2) (Table 2 and Fig. 2). Similarly, a significantly higher percentage of participants receiving icotrokinra than those receiving placebo reported a clinically

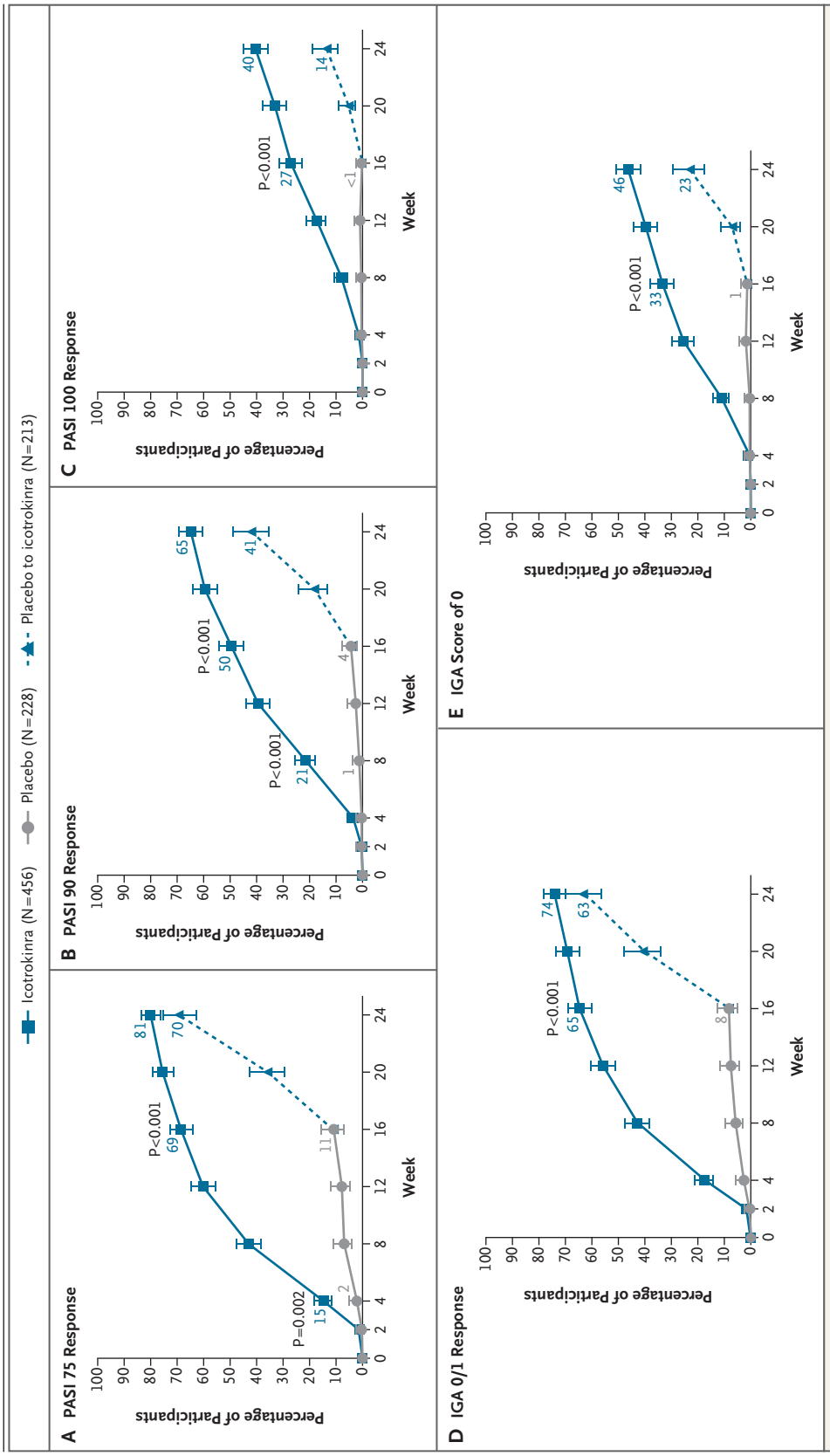

Figure 1. Coprimary and Key Secondary End Points with Respect to PASI Scores and IGA Scores.

Participants were randomly assigned (in a 2:1 ratio) to receive icotrokinra for 24 weeks or placebo for 16 weeks followed by transition to icotrokinra (placebo to icotrokinra). Scores on the Psoriasis Area and Severity Index (PASI) range from 0 to 72, with higher scores indicating a greater extent or severity of psoriasis. PASI 75 response, PASI 90 response, and PASI 100 response refer to reductions from baseline of at least 75%, 90%, and 100%, respectively, in the PASI score. Scores on the Investigator's Global Assessment (IGA) range from 0 (clear skin) to 4 (severe disease); a score of 1 indicates minimal disease. IGA 0/1 response refers to a score of 0 or 1 with a reduction from baseline of at least 2 points. P values are shown for the coprimary end points (PASI 90 response and IGA 0/1 response at week 16) and for several key secondary end points (PASI 75 response at week 4 and week 16, PASI 90 response at week 8, PASI 100 response at week 16, and IGA score of 0 at week 16). P values for key secondary end points were adjusted for multiplicity; details of multiplicity testing are provided in the Methods section in the Supplementary Appendix. I bars denote 95% confidence intervals.

meaningful improvement in the PSSD itch score at week 4 (19% vs. 5%; P=0.002), with an increased treatment effect through week 16 (58% vs. 13%; P<0.001) (mean change from baseline in the PSSD itch score, −3.9±2.7 vs. −0.7±2.5). Icotrokinra showed separation from placebo in a DLQI score of 0 or 1 by week 8 and continuing through week 16 (52% vs. 11%) (Fig. 2). Across participant-reported outcomes, the percentage of participants having a response to icotrokinra appeared to increase through week 24.

SAFETY FINDINGS

Through week 16, the incidence of adverse events was similar in the icotrokinra and placebo groups (49% in each group) (Table 3). The most common adverse events were nasopharyngitis (7% in each group) and upper respiratory

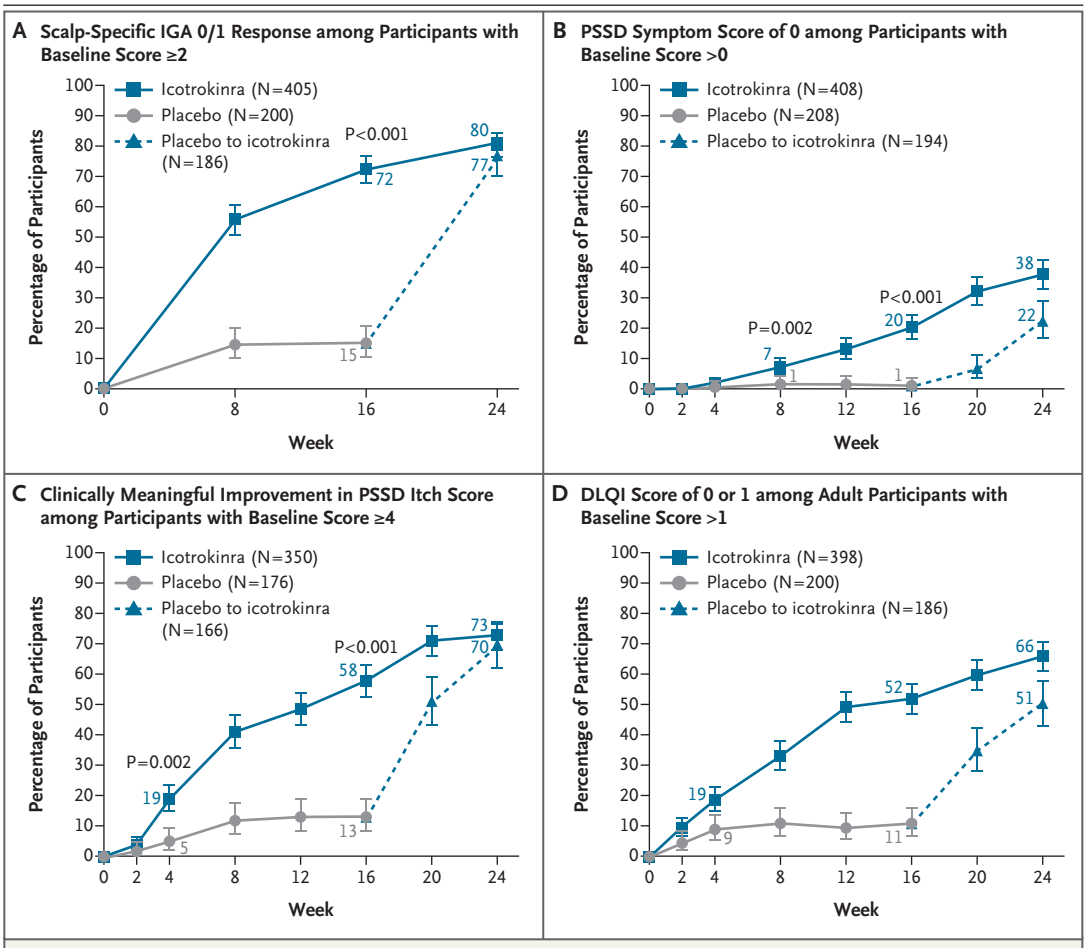

Figure 2. Other Key Secondary and Participant-Reported End Points.

Scalp-specific IGA scores range from 0 (absence of disease) to 4 (severe disease); a score of 1 indicates very mild disease. Scalp-specific IGA 0/1 response (Panel A) refers to a scalp-specific IGA score of 0 or 1 with a reduction from baseline of at least 2 points. Psoriasis Symptoms and Signs Diary (PSSD) symptom scores (Panel B) range from 0 to 100, with higher scores indicating a greater severity of symptoms. PSSD itch scores range from 0 to 10, with higher scores indicating a greater severity of itching; clinically meaningful improvement in the PSSD itch score (Panel C) refers to a reduction from baseline of at least 4 points. Scores on the Dermatology Life Quality Index (DLQI) (Panel D) range from 0 to 30, with higher scores indicating greater impairment in quality of life due to skin conditions. P values are shown for several key secondary end points (scalp-specific IGA 0/1 response at week 16, PSSD symptom score of 0 at week 8 and week 16, and clinically meaningful improvement in PSSD itch score at week 4 and week 16); a DLQI score of 0 or 1 at week 16 was an additional secondary end point. P values were adjusted for multiplicity; details of multiplicity testing are provided in the Methods section in the Supplementary Appendix. I bars denote 95% confidence intervals.

Table 3. Summary of Safety Assessments in Adult and Adolescent Participants through Week 16 and Week 24.

Variable	Icotrokinra, Weeks 0–16 (N=456)	Placebo, Weeks 0–16 (N=228)	Placebo to Icotrokinra, Weeks 16–24 (N=213)*	Icotrokinra, Weeks 0–24 (N=456)
Mean duration of follow-up — wk	15.9	15.8	8.2	23.6
Total participant-yr of follow-up	139.2	68.9	33.3	206.3
At least 1 adverse event — no. (%)†	225 (49)	112 (49)	53 (25)	253 (55)
No. per 100 participant-yr (95% CI)‡	234.5 (203.9–265.2)	239.8 (195.4–284.3)	182.4 (133.3–231.6)	199.1 (174.6–223.6)
Most common adverse events (≥5%) — no. (%)				
Nasopharyngitis	31 (7)	15 (7)	5 (2)	37 (8)
Upper respiratory tract infection	30 (7)	16 (7)	6 (3)	34 (7)
Headache	19 (4)	2 (<1)	0	21 (5)
Adverse event leading to discontinuation — no. (%)	6 (1)	1 (<1)	1 (<1)	6 (1)
No. per 100 participant-yr (95% CI)‡	4.3 (1.6–9.4)	1.5 (0.0–8.1)	3.0 (0.1–16.8)	2.9 (1.1–6.4)
Serious adverse event — no. (%)	6 (1)§	6 (3)§	1 (<1)¶	11 (2)¶
No. per 100 participant-yr (95% CI)‡	4.3 (1.6–9.4)	8.8 (3.2–19.2)	3.0 (0.1–16.8)	5.4 (2.7–9.6)
Gastrointestinal adverse event — no. (%)	26 (6)	13 (6)	1 (<1)	34 (7)
No. per 100 participant-yr (95% CI)‡	19.4 (12.7–28.5)	19.6 (10.5–33.6)	3.0 (0.1–16.8)	17.3 (12.0–24.2)
Infection — no. (%)†	107 (23)	51 (22)	21 (10)	131 (29)
No. per 100 participant-yr (95% CI)‡	89.2 (72.3–106.2)	85.5 (62.0–109.0)	66.3 (38.0–94.7)	77.6 (64.3–90.9)
Serious infection — no. (%)	1 (<1)	0	0	1 (<1)
No. per 100 participant-yr (95% CI)‡	0.7 (0.0–4.0)	0.0 (0.0–4.4)	0.0 (0.0–9.0)	0.5 (0.0–2.7)
Cancer — no. (%)	2 (<1)‖	0	0	2 (<1)‖
No. per 100 participant-yr (95% CI)‡	1.4 (0.2–5.2)	0.0 (0.0–4.4)	0.0 (0.0–9.0)	1.0 (0.1–3.5)
Active tuberculosis — no. (%)	0	0	0	0

* The data shown are for the period after participants transitioned from placebo to icotrokinra at week 16 and continuing through week 24.
† Details on types of adverse events, including infections, through week 16 and week 24 are provided in Table S5 and Table S6, respectively.
‡ Exposure-adjusted incidence rates were calculated as (number of participants with event/total participant-years at risk) × 100.
§ Serious adverse events through week 16 included adenocarcinoma of the colon, prostate cancer, pancreatitis, bacterial gastroenteritis, arthralgia, and subarachnoid hemorrhage in the icotrokinra group and acute cholecystitis, concussion, craniofacial fracture, pelvic fracture, worsening psoriasis, and hypertensive urgency in the placebo group.
¶ A serious adverse event involving worsening psoriasis occurred in the placebo-to-icotrokinra group during the period after week 16 and continuing through week 24. Serious adverse events through week 24 in the icotrokinra group included arthralgia, back pain, adenocarcinoma of colon, prostate cancer, hypertension, poor peripheral circulation, atrial fibrillation, pancreatitis, bacterial gastroenteritis, clavicle fracture, and subarachnoid hemorrhage.
‖ Cancers reported in the icotrokinra group were adenocarcinoma of the colon (one in a participant who had a history of smoking; the participant reported mild gastroenteritis during screening, severe colitis starting on trial 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 (one in a participant who had a history of smoking and a family history of prostate cancer; this participant had an elevated prostate-specific antigen level before baseline and received a diagnosis of grade 1 prostate cancer on trial day 48). Adverse-event narratives are provided in the Supplementary Appendix.

tract infection (7% in each group). Serious adverse events occurred in 1% of participants receiving icotrokinra and in 3% of those receiving placebo. The incidence of gastrointestinal adverse events (6% in each group), infections (23% in the icotrokinra group and 22% in the placebo group), and serious infections (<1% in the icotrokinra group and 0% in the placebo group) was similar in the two groups. In the icotrokinra group, cancer was reported early during treatment in two participants (<1%; colon adenocarcinoma in one participant with preexisting symptoms, and prostate cancer in one participant with an elevated prostate-specific antigen level before baseline; see adverse-event narratives in the Supplementary Appendix).

From weeks 0 through 16 and weeks 0 through 24 of icotrokinra treatment, exposure-adjusted incidence rates per 100 participant-years of follow-up remained stable for overall adverse events (234.5 and 199.1, respectively), including serious adverse events (4.3 and 5.4) and infections (89.2 and 77.6). No deaths were reported. Similar percentages of participants receiving icotrokinra and those receiving placebo had clinical laboratory abnormalities through week 16, without clinically relevant signals identified through week 24.

Adverse-event findings in the adolescent subgroup were consistent with those in the overall population. Through week 16, adverse events occurred in 50% of adolescents in the icotrokinra group and in 73% of those in the placebo group. The most common adverse events were nasopharyngitis (11% in the icotrokinra group and 14% in the placebo group) and upper respiratory tract infection (14% and 5%, respectively). Through week 24, the most common adverse events were similar to those observed through week 16.

Of 48 participants with latent tuberculosis infection (LTBI) at or before baseline, 20 participants (15 in the icotrokinra group and 5 in the placebo group) did not receive and 12 (7 and 5 in the respective groups) did receive concomitant treatment for LTBI at the investigator's discretion; 18 participants (11 in the icotrokinra group and 7 in the placebo group) were previously treated for LTBI. No cases of active or latent tuberculosis emerged during the treatment period.

DISCUSSION

The ICONIC-LEAD trial showed that once-daily icotrokinra, a systemic targeted oral peptide binding to the interleukin-23 receptor, was effective for treating plaque psoriasis in adults and in adolescents, an age group with limited systemic treatment options.[1,10,11,26] Treatment with icotrokinra resulted in a significantly higher incidence of skin clearance at week 16 than placebo. By week 24, nearly one half of participants receiving icotrokinra had complete skin clearance (IGA score of 0). Icotrokinra effectively cleared scalp psoriasis and relieved participant-reported psoriatic symptoms at week 16, with treatment effects evident as early as 4 weeks. The occurrence of adverse events, including gastrointestinal adverse events, was similar in the icotrokinra and placebo groups through week 16, with stable exposure-adjusted adverse-event rates and no safety signals identified through week 24.

Oral therapy offers advantages over injectable biologics, including greater patient preference and convenience.[3,4] However, given that most available oral therapies are less efficacious in treating plaque psoriasis than biologics,[5-8] patients with moderate-to-severe plaque psoriasis are generally limited to injectable therapies for the achievement of high-level efficacy with a favorable safety profile. The percentage of participants receiving icotrokinra who had clear skin at week 16 was within the range of percentages observed with FDA-approved injectable biologics targeting interleukin-23 for adults at week 12 or 16.[27-32] However, given the differences in trial populations, the percentages of participants with a placebo response, and statistical methods, definitive conclusions cannot be drawn about comparative efficacy. Moreover, the clinical-response findings from the ICONIC-LEAD trial complement those from the ongoing ICONIC-TOTAL trial[20] and are consistent with those of the previous phase 2 FRONTIER trials[18,19]; the similarity of these findings supports the appropriateness of dose selection. The absence of safety signals in the present trial and in the ICONIC-TOTAL trial was consistent with findings through 1 year in the FRONTIER trials.[18-20]

Strengths of the present trial include the large sample size across diverse geographic regions and age groups, which may be representative of patients with moderate-to-severe plaque psoriasis in real-world clinical practice. Imputation of nonresponse was used to address missing data; this method could underestimate the standard error and influence the estimated between-group differences. The trial excluded persons who had previous treatment failure with or an adverse event related to a biologic targeting interleukin-23, which potentially introduced selection bias. Although the trial-group assignments were blinded, participants were aware that those assigned to receive placebo would transition from placebo to icotrokinra at week 16, which may have influenced the rapid response observed in the placebo-to-icotrokinra group. This trial assessed clinical outcomes and participant-reported outcomes to comprehensively

evaluate the effect of icotrokinra, but it included a placebo control only through week 16 owing to ethical considerations and was not active comparator–controlled. Head-to-head comparison trials of icotrokinra and deucravacitinib[33] and a superiority trial of icotrokinra as compared with ustekinumab (ClinicalTrials.gov number, NCT06934226), a commonly prescribed biologic that targets both interleukin-12 and interleukin-23 and has a well-established benefit–risk profile, are being conducted. The ICONIC-LEAD trial is ongoing to collect data through 3 years, including rerandomized withdrawal and retreatment after week 24 in adults with a treatment response.

In this trial involving adults and adolescents with moderate-to-severe plaque psoriasis, selective blockade of the interleukin-23 receptor with the targeted oral peptide icotrokinra resulted in a significantly higher percentage of participants having skin clearance and reporting relief of symptoms than placebo at week 16. The incidence of adverse events with icotrokinra was similar to that with placebo. Longer-term data will provide a more complete understanding of the benefit–risk profile of icotrokinra.

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