

ORIGINAL ARTICLE

A Human Interleukin-12/23 Monoclonal Antibody for the Treatment of Psoriasis

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ABSTRACT

BACKGROUND

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Skin-infiltrating lymphocytes expressing type 1 cytokines have been linked to the pathophysiology of psoriasis. We evaluated the safety and efficacy of a human interleukin-12/23 monoclonal antibody in treating psoriasis.

METHODS

In this double-blind, placebo-controlled trial, 320 patients with moderate-to-severe plaque psoriasis underwent randomization to treatment with the interleukin-12/23 monoclonal antibody (one 45-mg dose, one 90-mg dose, four weekly 45-mg doses, or four weekly 90-mg doses) or placebo; 64 patients were randomly assigned to each group. Patients assigned to the interleukin-12/23 monoclonal antibody received one additional dose at week 16 if needed. Patients assigned to placebo crossed over to receive one 90-mg dose of interleukin-12/23 monoclonal antibody at week 20.

*The investigators for the CNTO 1275 Psoriasis Study Group are listed in the Appendix.

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RESULTS

There was at least 75% improvement in the psoriasis area-and-severity index at week 12 (the primary end point) in 52% of patients who received 45 mg of the interleukin-12/23 monoclonal antibody, in 59% of those who received 90 mg, in 67% of those who received four weekly 45-mg doses, and in 81% of those who received four weekly 90-mg doses, as compared with 2% of those who received placebo ($P < 0.001$ for each comparison), and there was at least 90% improvement in 23%, 30%, 44%, and 52%, respectively, of patients who received the monoclonal antibody as compared with 2% of patients who received placebo ($P < 0.001$ for each comparison). Adverse events occurred in 79% of patients treated with the interleukin-12/23 monoclonal antibody as compared with 72% of patients in the placebo group ($P = 0.19$). Serious adverse events occurred in 4% of patients who received the monoclonal antibody and in 1% of those who received placebo ($P = 0.69$).

CONCLUSIONS

This study demonstrates the therapeutic efficacy of an interleukin-12/23 monoclonal antibody in psoriasis and provides further evidence of a role of the interleukin-12/23 p40 cytokines in the pathophysiology of psoriasis. Larger studies are needed to determine whether serious adverse events might limit the clinical usefulness of this new therapeutic target. (ClinicalTrials.gov number, NCT00320216.)

PSORIASIS IS A CHRONIC INFLAMMATORY skin disorder affecting 2 to 3% of the world's population.^{1,2} Psoriasis affects the physical and emotional well-being of patients, and its effect on quality of life is similar to that seen with other major medical diseases.³ Significant unmet need remains for safe, highly effective, and convenient treatments. Aberrant type 1 immune responses have been linked to the pathogenesis of psoriasis,⁴⁻⁷ and cytokines that elicit these immune responses (e.g., interleukin-12 and interleukin-23) may represent appropriate therapeutic targets.⁸ Interleukin-12 p40 is overexpressed in psoriasis plaques,⁹ and preclinical studies implicate this cytokine in the pathogenesis of psoriasis.^{10,11} Interleukin-23, which also shares the p40 subunit and is overexpressed in psoriasis plaques,^{12,13} activates a distinct T-cell lineage that expresses interleukin-17 and that may be pathogenically important.^{14,15}

To evaluate the therapeutic effect of blocking interleukin-12 and interleukin-23, a fully human interleukin-12/23 monoclonal antibody (CNTO 1275) was developed. This antibody binds with high affinity to the p40 subunit of human interleukin-12 and interleukin-23, neutralizing their bioactivity by blocking interactions with their cognate cell-surface receptors. Early clinical studies showed no dose-limiting toxic effects and suggested potential therapeutic efficacy in certain immune-mediated diseases.¹⁶⁻¹⁸ This phase 2 study evaluated the safety and efficacy of the interleukin-12/23 monoclonal antibody in patients with moderate-to-severe psoriasis.

METHODS

PATIENTS

This study was conducted at 46 sites worldwide after approval of the institutional review boards. The first patient consented to participation on June 25, 2003, and the last patient visit occurred on March 9, 2005. After providing written informed consent, men and women (age, ≥ 18 years) were eligible if they had a diagnosis of plaque psoriasis for at least 6 months, were candidates for phototherapy or systemic therapy, had a baseline score on the psoriasis area-and-severity index of 12 or higher (on a scale of 0 to 72, with higher scores indicating more severe disease), and had involvement of at least 10% body-surface area.

Patients were ineligible if they had nonplaque forms of psoriasis; had a recent serious systemic

or local infection; had active or latent tuberculosis, asthma, or a known malignancy within the previous 5 years (except treated basal-cell skin cancer); had received previous treatment with any agent specifically targeting interleukin-12 or interleukin-23; had received biologic or investigational agents within the previous month or five drug half-lives; had received conventional systemic psoriasis therapy or phototherapy within the previous 4 weeks; or had received topical psoriasis treatment within the previous 2 weeks.

STUDY DESIGN

This placebo-controlled, double-blind, parallel-group, phase 2 study evaluated the safety and efficacy of single and multiple doses of the interleukin-12/23 monoclonal antibody for the treatment of psoriasis. With the use of adaptive treatment allocation based on a biased-coin minimization algorithm,¹⁹ patients were randomly assigned to one 45-mg subcutaneous dose of the interleukin-12/23 monoclonal antibody, one 90-mg dose, four weekly 45-mg doses, four weekly 90-mg doses, or placebo. Randomization was stratified by investigational site and by the weight of the patient relative to 95 kg. At week 16, patients with a physician's global assessment (termed PGA) of less than excellent (≥ 3 on a scale on which 1 is best and 6 is worst) received one additional injection of their originally assigned dose. At week 20, patients in the placebo group crossed over to receive one 90-mg injection of the interleukin-12/23 monoclonal antibody.

EFFICACY AND SAFETY EVALUATIONS

Efficacy evaluations were performed through week 32. The psoriasis area-and-severity index (termed PASI) combines assessments of the extent of body-surface involvement in four anatomical regions (head, trunk, arms, and legs) and the severity of desquamation, erythema, and plaque induration (thickness) in each region, yielding an overall score of 0 (no psoriasis) to 72 (severe disease).²⁰ The physician's global assessment rates the patient's psoriasis overall relative to baseline as 1 (clear), 2 (excellent), 3 (good), 4 (fair), 5 (poor), or 6 (worse) and considers involvement of body-surface area, induration, scaling, and erythema. The 10-item Dermatology Life Quality Index questionnaire, completed by the patient, measures whether psoriasis has an effect on the patient's quality of life, with scores ranging from 0 ("not at all") to 30 ("very much").

We assessed the safety and tolerability of the interleukin-12/23 monoclonal antibody by monitoring adverse events and routine laboratory values through week 36. Serum samples collected through week 52 were tested for antibodies to the interleukin-12/23 monoclonal antibody with the use of an antigen-bridging enzyme immunoassay.¹⁶

STATISTICAL ANALYSIS

Efficacy data from all patients who underwent randomization were analyzed according to the treatment group. Missing values at week 12 were replaced with the most recently available values for all efficacy variables; missing data at other time points were not imputed. Patients in the placebo group were included in efficacy summaries after week 20 if they had crossed over to receive the interleukin-12/23 monoclonal antibody. Safety data were summarized according to the actual treatment received.

The data-analysis plan was specified before the treatment assignments were revealed. According to these prespecified rules, the proportions of patients responding to treatment were compared using the Cochran–Mantel–Haenszel chi-square test stratified according to low and high body weight. Continuous response variables were compared with the use of analysis of covariance for van der Waerden normal scores²¹ with weight as a binary covariate. We used Fisher's exact test to compare safety-event rates. All statistical tests were two-sided and were performed at an alpha level of 0.05.

The primary efficacy end point — the proportion of patients achieving at least 75% improvement from baseline in the psoriasis area-and-severity index at week 12 — was analyzed on an intention-to-treat basis to include data from all patients who had undergone randomization; no interim analyses were performed. Patients who discontinued study treatment because of lack of efficacy or loss of response or who used prohibited medications were considered to have had no response. An overall type I error rate of 0.05 was maintained by performing four pairwise comparisons, one between each active-treatment group and placebo sequentially, from the group that received the highest dose to the group that received the lowest dose of the interleukin-12/23 monoclonal antibody.²² If a comparison was not significant at an alpha level of 0.05, subsequent

Figure 1 (facing page). Enrollment and Treatment of Patients in the Study.

At week 16, all patients in the active-treatment groups who had a physician's global assessment of 3 or higher received the assigned treatment, and those who had an assessment of less than 3 received placebo. The placebo group at week 16 does not include one patient who received a single 90-mg dose of interleukin-12/23 monoclonal antibody. At week 20, all patients in the placebo group were expected to receive a single 90-mg dose of interleukin-12/23 monoclonal antibody, but one patient received placebo in error.

sequential comparisons were considered nonsignificant. Assuming 60 patients per group and response rates of 50% for each treatment group and 10% for the placebo group, this study had more than 99% power at the 5% level of significance to detect at least one pairwise treatment effect.

The steering committee of the CNTO 1275 Psoriasis Study Group and Centocor designed and conducted this study. Centocor analyzed the data, and the steering committee and Centocor jointly interpreted the data and contributed to the manuscript. The academic authors had full access to the data, and all authors vouch for the integrity and completeness of the data and analyses.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Most of the 320 patients randomly assigned to the five trial groups (Fig. 1) were men. Baseline demographics and disease characteristics were similar among the trial groups (Table 1). Among the five groups, the average body-surface area affected by psoriasis was approximately 25% and the average duration of psoriasis ranged from approximately 17 to 20 years.

EFFICACY

Thirty-three of 64 patients (52%) treated with one 45-mg dose of the interleukin-12/23 monoclonal antibody, 38 of 64 (59%) treated with one 90-mg dose, 43 of 64 (67%) treated with four weekly 45-mg doses, and 52 of 64 (81%) treated with four weekly 90-mg doses had at least 75% improvement in the psoriasis area-and-severity index at week 12 (the primary end point), as compared with only 1 of 64 patients (2%) receiving placebo ($P < 0.001$ for each comparison) (Table 2

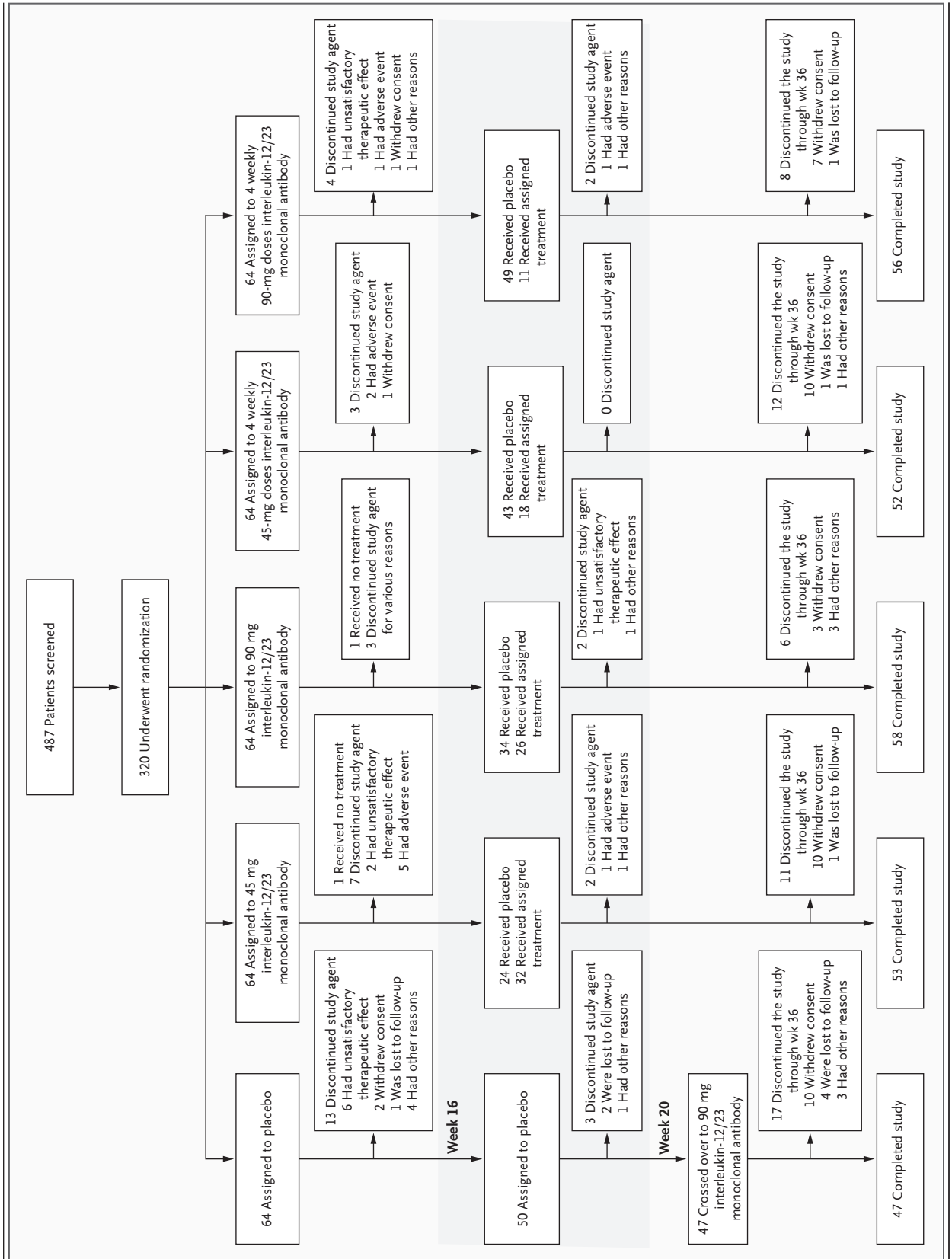


Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N=64)	Interleukin-12/23 Monoclonal Antibody (N=256)				P Value†
		45 mg (N=64)	90 mg (N=64)	4× 45 mg (N=64)	4× 90 mg (N=64)	
Age — yr	44±14	46±14	46±13	45±12	44±13	0.75
Male sex — no. (%)	46 (72)	38 (59)	47 (73)	39 (61)	52 (81)	0.04‡
Weight — kg	92.8±20.8	94.3±25.5	92.9±19.1	92.8±22.6	91.9±25.7	0.97
Duration of psoriasis — yr	16.9±11.0	19.1±12.3	17.9±11.6	19.8±11.9	17.3±13.5	0.43
Involved body-surface area — %	26.6±18.4	28.5±16.6	26.3±17.6	27.4±16.9	27.4±18.1	0.80
Patients with psoriatic arthritis — no. (%)	12 (19)	13 (20)	12 (19)	12 (19)	13 (20)	1.00
Psoriasis area-and-severity index score	19.9±8.3	19.0±7.4	18.8±7.3	18.9±7.0	19.0±7.9	0.97
Dermatology Life Quality Index score	12.0±7.2	11.9±7.0	13.4±7.3	12.6±6.6	10.5±6.7	0.15
Patients treated previously — no. (%)§						
Topical agent	61 (95)	63 (98)	63 (98)	60 (94)	59 (92)	0.31
Systemic therapy	39 (61)	39 (61)	37 (58)	46 (72)	35 (55)	0.34

* Plus-minus values are means ±SD.

† To identify any significant differences in demographic and baseline characteristics among the treatment groups, we calculated P values using the chi-square test for categorical variables and an analysis of variance for van der Waerden normal scores for continuous variables.

‡ No significant differences in sex were found between the placebo group and each of the active-treatment groups. However, significant differences in sex were found between the group receiving 45 mg of interleukin-12/23 monoclonal antibody and the group receiving four weekly 90-mg doses ($P=0.007$), as well as between the group receiving four weekly 45-mg doses and the group receiving four weekly 90-mg doses ($P=0.01$).

§ According to the protocol, all topical therapies (except moisturizers and shampoos) had to be discontinued 2 weeks before randomization, and all systemic therapies 4 weeks before randomization.

and Fig. 2A). Similar proportions of patients were assessed as being clear or having an excellent response according to physicians' global assessments, with all active-treatment groups significantly improved as compared with the placebo group ($P<0.001$ for each comparison) (Table 2 and Fig. 2B).

Marked clinical responses were observed in significantly more patients in each active-treatment group than in the placebo group, as measured by at least 90% improvement in the psoriasis area-and-severity index at week 12 ($P<0.001$ for each comparison) (Table 2 and Fig. 2D). Significantly more patients in the three higher-dose groups than in the placebo group had 100% improvement in the psoriasis area-and-severity index or had a physician's global assessment of clear ($P\leq 0.001$ for each comparison with placebo) (Table 2). At least 75% of patients in all active-treatment groups had at least 50% improvement in the psoriasis area-and-severity index score ($P<0.001$ for each comparison with placebo) (Table 2 and Fig. 2C). The percentage improvements in the psoriasis area-and-severity index score from baseline were significant for all active-treatment

groups by week 2 ($P<0.001$ for each comparison with placebo).

The Dermatology Life Quality Index showed significant improvements in quality of life for all active-treatment groups at week 12 ($P<0.001$ for each comparison with placebo) (Table 2) and week 24 (Fig. 2E). Significantly more patients in all active-treatment groups reported that their psoriasis had no measurable effect on their quality of life, as indicated by a Dermatology Life Quality Index score of 0 at week 12 ($P<0.001$ for each comparison with placebo) (Table 2).

Of 237 patients in the interleukin-12/23 monoclonal antibody groups continuing study treatments at week 16, only 87 patients (37%) were eligible to receive one additional dose at week 16 on the basis of a response of less than excellent according to physicians' global assessments (Fig. 1). Nevertheless, the proportions of patients with at least 50%, 75%, and 90% improvement in the psoriasis area-and-severity index or with an excellent response or better according to physicians' global assessments remained relatively stable through week 24 (Fig. 2A through 2D). Response rates declined after treatment was discontinued.

Table 2. Clinical Responses at Week 12 as Reported by Physicians and Patients.*

Variable	Placebo (N=64)	Interleukin-12/23 Monoclonal Antibody (N=256)			
		45 mg (N=64)	90 mg (N=64)	45 mg (N=64)	90 mg (N=64)
Reported by the physician					
Psoriasis area-and-severity index score					
Mean \pm SD	16.4 \pm 8.1	6.5 \pm 6.6	5.7 \pm 7.0	3.6 \pm 4.2	3.0 \pm 3.7
Median	15.0	3.7	3.2	2.4	1.8
Interquartile range	10.1 to 20.6	2.0 to 9.9	1.3 to 7.0	0.8 to 5.2	0.7 to 3.4
P value		<0.001	<0.001	<0.001	<0.001
Improvement in psoriasis area-and-severity index score					
At least 50% — no. (%)	7 (11)	48 (75)	52 (81)	59 (92)	59 (92)
P value		<0.001	<0.001	<0.001	<0.001
At least 75% — no. (%) †	1 (2)	33 (52)	38 (59)	43 (67)	52 (81)
P value		<0.001	<0.001	<0.001	<0.001
At least 90% — no. (%)	1 (2)	15 (23)	19 (30)	28 (44)	33 (52)
P value		<0.001	<0.001	<0.001	<0.001
100% — no. (%)	0	3 (5)	10 (16)	10 (16)	13 (20)
P value		NC	0.001	0.001	<0.001
Physician's global assessment					
"Clear" or "excellent" — no. (%)	0	32 (50)	34 (53)	46 (72)	53 (83)
P value		<0.001	<0.001	<0.001	<0.001
"Clear" — no. (%)	0	4 (6)	11 (17)	10 (16)	15 (23)
P value		NC	<0.001	0.001	<0.001
Reported by the patient					
Change in Dermatology Life Quality Index score					
Mean \pm SD	-2.2 \pm 4.2	-7.4 \pm 6.2	-9.8 \pm 7.0	-10.2 \pm 6.8	-8.4 \pm 6.2
Median	-1.0	-6.0	-10.0	-9.0	-8.0
Interquartile range	-5.0 to 0.0	-12.0 to -3.0	-13.0 to -5.0	-14.0 to -5.5	-12.0 to -4.0
P value		<0.001	<0.001	<0.001	<0.001
Dermatology Life Quality Index score of 0 — no. (%)	1 (2)	13 (20)	19 (30)	27 (42)	26 (41)
P value		<0.001	<0.001	<0.001	<0.001

* All P values are for the comparison with placebo. NC denotes not calculated.

† The primary efficacy measure was an improvement from baseline of at least 75% in the psoriasis area-and-severity index at week 12. Seventeen patients had missing week 12 scores, which were replaced with the most recently available previous score. Of these 17 patients, 16 did not reach the primary end point and 1 (in the group receiving four weekly 45-mg doses of the interleukin-12/23 monoclonal antibody) was considered to have reached the primary end point.

Efficacy in those patients in the placebo group who received one 90-mg injection of the interleukin-12/23 monoclonal antibody at week 20 mirrored the improvements observed in patients originally assigned to one 90-mg dose at baseline (Fig. 2A through 2D).

SAFETY

Through week 20 (the placebo-controlled portion of the study), 79% of patients who received active treatment had adverse events (mean duration of follow-up, 19.7 weeks) as compared with 72% who received placebo (mean duration of follow-up,

17.9 weeks; $P=0.19$). Adverse events leading to the discontinuation of treatment occurred in 4% of patients who received active treatment as compared with 3% who received placebo ($P=1.00$). Forty-three percent of patients who received active treatment and 39% of patients who received placebo had infections. We observed no obvious association between a higher dose and an increased rate of adverse events or infections. Serious adverse events,²³ all of which were classified as serious because the patients required hospitalization, were observed in 4% of patients treated with the interleukin-12/23 monoclonal antibody (9 of 252) and 1% of patients in the placebo group (1 of 67, $P=0.69$). In the groups that received the interleukin-12/23 monoclonal antibody, two patients were hospitalized for infection (one for cellulitis and one for pneumonia), two patients (a 61-year-old man with diabetes and hypertension and a 54-year-old man with diabetes) had myocardial infarctions and required coronary bypass surgery for multivessel coronary artery disease, and one patient (a 59-year-old woman with hypertension and hyperlipidemia) had a stroke and subsequently underwent endarterectomy. In the placebo group, one serious adverse event (aggravated psoriasis) resulted in hospitalization. One patient (1%) in the placebo group had basal-cell skin cancer, and three patients (2%) who received the interleukin-12/23 monoclonal antibody had cancer (one had basal-cell skin cancer, one squamous-cell skin cancer, and one prostate cancer). Injection-site reactions were observed in 2% of injections of the interleukin-12/23 monoclonal antibody (17 of 706) and 2% of injections of placebo (17 of 819) (Table 3).

Through week 20, the proportions of patients who had significant abnormalities in laboratory values for hematologic and blood chemical tests were low and similar between the groups receiving active treatment and the placebo group. A nonsignificantly greater proportion of patients treated with the interleukin-12/23 monoclonal antibody than with placebo had elevated glucose levels while in a nonfasting state (24 of 252 [10%] vs. 3 of 67 [4%], $P=0.23$). No significant differences between the active-treatment groups and the placebo group were observed in changes in absolute lymphocyte counts or lymphocyte subsets (data not shown).

Adverse events observed in the overall study population after patients in the placebo group crossed over were similar to the pattern of ad-

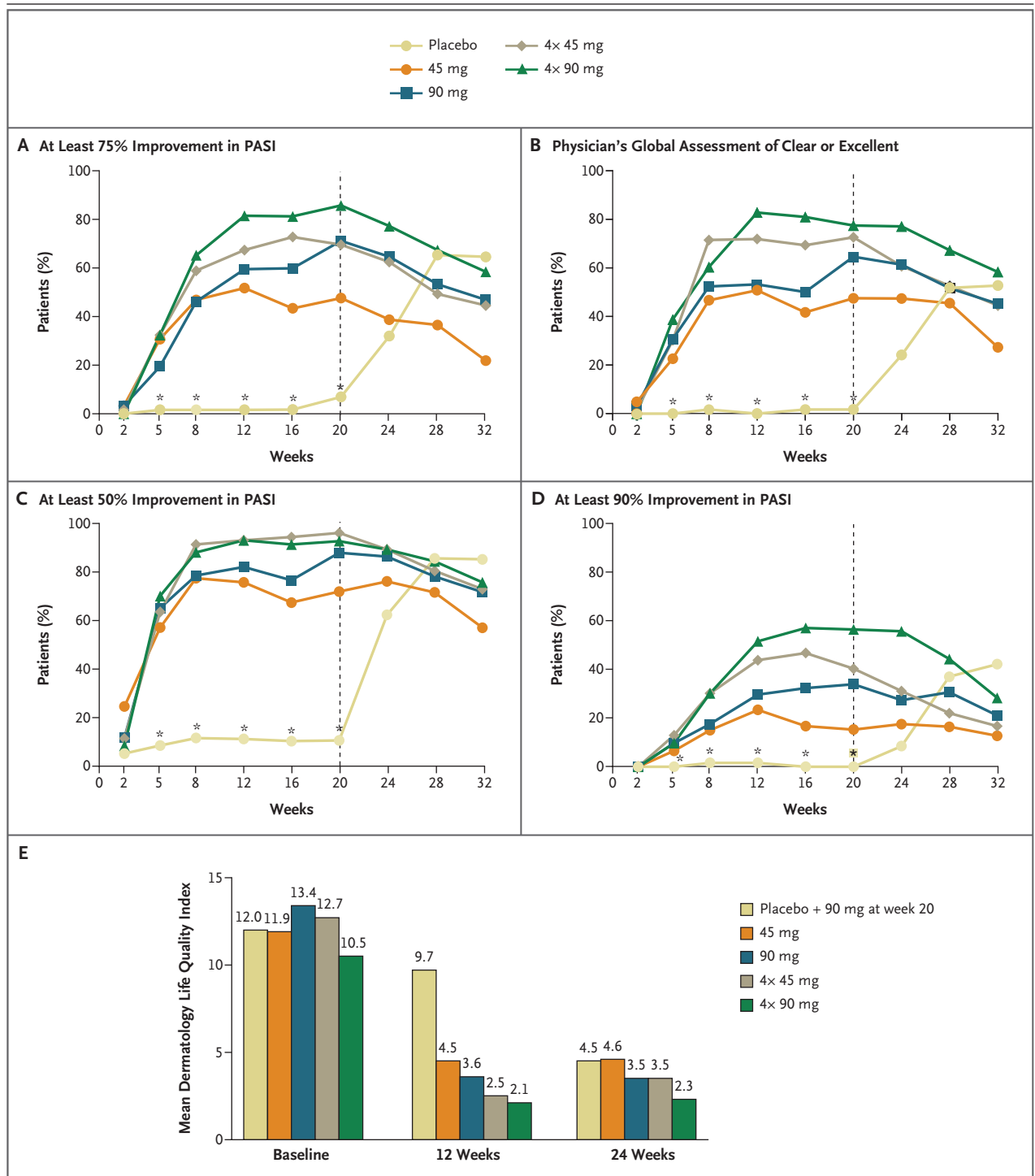
Figure 2. Clinical Response to the Interleukin-12/23 Monoclonal Antibody, as Measured by the Psoriasis Area-and-Severity Index (PASI) and the Physician's Global Assessment over Time.

Panel A shows the percentage of patients who had at least 75% improvement in the psoriasis area-and-severity index during the trial, and Panel B shows the percentage of patients who had a physician's global assessment score of "clear" or "excellent." Panel C shows the percentage of patients who had at least 50% improvement in the psoriasis area-and-severity index, and Panel D shows the percentage of patients who had at least 90% improvement. Asterisks indicate statistically significant differences between each active-treatment group and placebo. The dashed vertical line shows the time at which the placebo group crossed over to receive one dose of the interleukin-12/23 monoclonal antibody. At week 16, because of a physician's global assessment score of less than excellent, 32 of 64 patients in the group receiving 45 mg of interleukin-12/23 monoclonal antibody, 26 of 64 patients in the 90-mg group, 18 of 64 in the group receiving four weekly 45-mg doses, and 11 of 64 in the group receiving four weekly 90-mg doses received one additional dose of the interleukin-12/23 monoclonal antibody at their randomly assigned dose. Of 64 patients randomly assigned to placebo, 47 patients crossed over to receive a single 90-mg dose of the interleukin-12/23 monoclonal antibody at week 20. Panel E shows mean scores on the Dermatology Life Quality Index at baseline, 12 weeks, and 24 weeks (lower scores indicate better quality of life).

verse events observed during the placebo-controlled portion of the study. A small number of patients had serious adverse events, including one occurrence each of coronary artery disorder, congestive heart failure, viral syndrome, urinary tract infection, cellulitis in a surgical wound, and elevated liver-enzyme levels. In addition, the patient in the placebo group in whom basal-cell skin cancer was diagnosed had a second basal-cell cancer reported after crossover to active treatment. Of the 293 patients treated with the interleukin-12/23 monoclonal antibody, antibodies to the study agent were detectable in 12 patients (4%) once or more during the 52 weeks of monitoring for these antibodies. Neither the presence of nor the levels of antibodies were associated with injection-site reactions.

DISCUSSION

Our findings demonstrate the efficacy and adverse-event profile of an interleukin-12/23 monoclonal antibody in the treatment of psoriasis. They also establish a central role for the interleukin-12/23 p40 cytokines in the pathophysiology of psoria-



sis. The percentage of patients who had at least 75% improvement in the psoriasis area-and-severity index at week 12 increased in a dose-dependent manner. Marked clearance of psoriatic skin lesions was noted in many patients; significant proportions of patients had at least 90% improve-

ment in the psoriasis area-and-severity index, and significant proportions of patients had complete clearance of psoriasis. Almost all patients had clinically meaningful improvement, as measured by 50% improvement in the psoriasis area-and-severity index.²⁴

Table 3. Adverse Events during the Placebo-Controlled Phase (Weeks 0 to 20) and through the End of the Study (Weeks 0 to 36).*

Variable	Weeks 0 to 20				Weeks 0 to 36			
	Placebo (N=67)	45 mg (n=63)	90 mg (n=64)	4x 45 mg (n=63)	Interleukin-12/23 Monoclonal Antibody (n=62) all four active-treatment groups	Placebo (0-20 wk) (N=67)	Placebo Crossover to 90-mg Active Treatment (20-36 wk) (N=49)	All Four Active-Treatment Groups (0-36 wk) (N=252)
Mean duration of follow-up — wk	17.9	19.4	19.3	20.0	20.1	17.9	16.9	35.1
Patients with at least 1 adverse event — no. (%)†	48 (72)	57 (90)	52 (81)	49 (78)	42 (68)	48 (72)	25 (51)	216 (86)
Common adverse events — no. of patients (%)‡								
Upper respiratory tract infection	14 (21)	16 (25)	20 (31)	9 (14)	11 (18)	14 (21)	6 (12)	78 (31)
Headache	11 (16)	12 (19)	12 (19)	2 (3)	9 (15)	11 (16)	1 (2)	38 (15)
Pain	2 (3)	3 (5)	8 (12)	3 (5)	4 (6)	2 (3)	4 (8)	22 (9)
Sinusitis	3 (4)	3 (5)	4 (6)	3 (5)	3 (5)	3 (4)	1 (2)	20 (8)
Injury	4 (6)	2 (3)	3 (5)	1 (2)	2 (3)	4 (6)	1 (2)	19 (8)
Pruritus	2 (3)	6 (10)	3 (5)	5 (8)	3 (5)	2 (3)	0	18 (7)
Rhinitis	3 (4)	4 (6)	5 (8)	5 (8)	1 (2)	3 (4)	1 (2)	18 (7)
Diarrhea	0	3 (5)	4 (6)	4 (6)	2 (3)	0	1 (2)	17 (7)
Myalgia	2 (3)	4 (6)	4 (6)	3 (5)	1 (2)	2 (3)	0	15 (6)
Fatigue	1 (1)	3 (5)	3 (5)	2 (3)	3 (5)	1 (1)	0	14 (6)
Purpura	2 (3)	4 (6)	5 (8)	1 (2)	3 (5)	2 (3)	0	14 (6)
Urinary tract infection	0	3 (5)	1 (2)	2 (3)	2 (3)	0	0	14 (6)
Nausea	3 (4)	1 (2)	4 (6)	1 (2)	4 (6)	3 (4)	1 (2)	13 (5)
Pharyngitis	4 (6)	1 (2)	1 (2)	5 (8)	3 (5)	4 (6)	2 (4)	12 (5)
Back pain	0	3 (5)	2 (3)	4 (6)	1 (2)	0	0	10 (4)
Aggravated psoriasis	4 (6)	2 (3)	0	0	1 (2)	4 (6)	0	7 (3)
Aggravated arthritis	5 (7)	1 (2)	0	1 (2)	0	5 (7)	0	3 (1)
Adverse events leading to withdrawal of study agent — no. of patients (%)†	2 (3)	8 (13)	1 (2)	1 (2)	1 (2)	2 (3)	0	12 (5)
Serious adverse events — no. of patients (%)†‡	1 (1)	3 (5)	1 (2)	2 (3)	3 (5)	1 (1)	1 (2)	13 (5)
Myocardial infarction	0	0	1 (2)	0	1 (2)	0	0	2 (1)
Psychosis secondary to methamphetamine use	0	1 (2)	0	0	0	0	0	2 (1)
Coronary-artery disorder	0	0	0	0	0	0	0	1 (<1)

Chest pain from noncardiac causes	0	0	0	1 (2)	0	1 (<1)	0	0	1 (<1)
Injury	0	1 (2)	0	0	0	1 (<1)	0	0	1 (<1)
Cellulitis	0	1 (2)	0	0	0	1 (<1)	0	0	1 (<1)
Uterine fibroid	0	0	0	0	1 (2)	1 (<1)	0	0	1 (<1)
Drug dependence	0	0	0	0	0	0	0	0	1 (<1)
Cardiac failure	0	0	0	0	0	0	0	0	1 (<1)
Congenital hernia	0	0	0	0	0	0	0	0	1 (<1)
Viral infection	0	0	0	0	0	0	0	0	1 (<1)
Pneumonia	0	0	0	0	1 (2)	1 (<1)	0	0	1 (<1)
Urinary tract infection	0	0	0	0	0	0	0	0	1 (<1)
Cerebral infarction	0	0	0	1 (2)	0	1 (<1)	0	0	1 (<1)
Aggravated psoriasis	1 (2)	0	0	0	0	1 (<1)	1 (2)	0	1 (<1)
Hepatic enzymes increased	0	0	0	0	0	0	0	1 (2)	0
Adverse events of special interest									
Infections — no. of patients (%)†	26 (39)	35 (56)	28 (44)	27 (43)	19 (31)	109 (43)	26 (39)	11 (22)	142 (56)
Cancer — no. of patients (%)‡									
Cutaneous¶	1 (1)	1 (2)	0	0	1 (2)	2 (1)	1 (1)	1 (2)	2 (1)
Noncutaneous	0	1 (2)	0	0	0	1 (<1)	0	0	1 (<1)
Injection-site reactions — no./total no. (%)**									
Placebo	3/303 (1)	6/203 (3)	7/220 (3)	0/43	1/50 (2)	14/516 (3)	3/303 (1)	0/2	14/742 (2)
Interleukin-12/23 monoclonal antibody	NA	4/94 (4)	3/89 (3)	6/270 (2)	4/253 (2)	17/706 (2)	NA	0/50	17/707 (2)

* Safety data include only those patients who received at least one injection of study agent and were summarized according to the actual treatment received. One patient did not undergo randomization but was treated with placebo at week 0, and two patients were never treated.

† Significant differences were not observed in the rates of patients who had at least one adverse event (P=0.19), adverse events leading to withdrawal of the study agent (P=1.00), serious adverse events (P=0.69), infections (P=0.51), or malignant conditions (P=1.00), although the study was not designed or powered to detect small differences in rates of adverse events. All statistical comparisons for common adverse events resulted in P values exceeding 0.05, with the exception of that for cases of aggravated psoriasis (P=0.04) and aggravated arthritis (P=0.005), both of which occurred more commonly in the placebo group.

‡ Common adverse events were those occurring in at least 5% of patients in any treatment group.

§ A serious adverse event was defined as any adverse event that resulted in any of the following outcomes: death, a life-threatening condition, in-patient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or a congenital anomaly or birth defect, regardless of its relationship to the study agent.²³

¶ Cutaneous cancers include squamous-cell and basal-cell carcinomas.

|| Noncutaneous cancer is prostate cancer.

** There were a total of 819 injections of placebo and 706 injections of interleukin-12/23 monoclonal antibody. Maintaining the double-blind aspect of the study required that patients randomly assigned to treatment with the interleukin-12/23 monoclonal antibody receive placebo at dosing visits when they were not scheduled to receive the study agent. NA denotes not applicable.

Patient-reported outcome measures improved significantly in patients treated with the interleukin-12/23 monoclonal antibody. Significantly more patients treated with the interleukin-12/23 monoclonal antibody than with placebo reported improvement of their overall skin condition at week 12, and this improvement was accompanied by quality-of-life improvements reflected in the Dermatology Life Quality Index. Many patients indicated that psoriasis had no detectable adverse effect on their quality of life after active treatment. Elevated levels of interleukin-12 have been associated with major depression.²⁵ Whether quality-of-life improvements resulted from a reduction in the levels of interleukin-12, independent of improvements in overall skin condition, warrants further evaluation.

The proportions of patients who had adverse events and serious adverse events were higher among patients treated with the interleukin-12/23 monoclonal antibody than among those treated with placebo; the differences were not statistically significant, but the trial was not large enough to detect differences in uncommon serious adverse events. Rates of injection-site reactions were similar between patients treated with the interleukin-12/23 monoclonal antibody and those who received placebo. Development of antibodies to the interleukin-12/23 monoclonal antibody occurred in 4% of patients. The relationship between treatment with the interleukin-12/23 monoclonal antibody and glucose abnormalities in nonfasting patients, cancer, and the serious adverse events observed (including serious infections and myocardial infarctions) requires further study. Neither tuberculosis nor opportunistic infections developed in any patients, although both have been reported in persons congenitally deficient in interleukin-12 p40 or interleukin-12 receptor β 1.^{26,27} The moderate size of the study precludes meaningful assessment of the effect that blocking interleukin-12 and interleukin-23 can have on the risk of cancer. Preclinical models suggest that the interleukin-12/23 p40 cytokines play a role in tumor immunity, though it remains unclear whether blocking the interleukin-12 and interleukin-23 cytokines will affect the risk of cancer in humans or whether any effects would be detrimental or potentially protective.²⁸⁻³⁰

Our findings support previous studies showing an immune basis for psoriasis.^{4-6,31,32} The high proportion of patients responding to the in-

terleukin-12/23 monoclonal antibody and the high level of response of the patients implicate the p40 subunit, shared by the interleukin-12 and interleukin-23 cytokines, as a key mediator of psoriasis. Produced by antigen-presenting cells, such as Langerhans' cells in the skin, interleukin-12 activates CD4+ T cells and natural killer cells to induce expression of type 1 cytokines, such as interferon- γ and tumor necrosis factor α , which have been shown to be important in the pathophysiology of psoriasis.³³ Interleukin-23 activates a distinct T-cell lineage that expresses interleukin-17 and increases keratinocyte expression of inducible nitric oxide synthase, which has also been implicated in the pathophysiology of psoriasis.³⁴ The relative contributions of interleukin-12 and interleukin-23 to the pathophysiology of psoriasis are incompletely understood, though recent evidence supports a prominent role of interleukin-23.¹²

These results indicate that the interleukin-12/23 p40 cytokines may be an important new therapeutic target for patients with psoriasis. Although we recognize the limitations of comparisons across studies, the high level of efficacy observed in this study compares favorably with the efficacy reported for currently available intramuscularly or subcutaneously administered biologic therapeutics for psoriasis.^{6,31,32} Administration of the interleukin-12/23 monoclonal antibody led to pharmacodynamic effects that were sustained for many weeks and provided significant and prolonged efficacy after only one dose or four weekly doses. This trial was not designed to evaluate the efficacy and safety of long-term use. Additional studies are needed to characterize the safety and efficacy of the interleukin-12/23 monoclonal antibody in patients with psoriasis and to define the dose schedule that will safely maintain the high level of response.

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APPENDIX

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