A Randomized Trial of Ustekinumab, a Human Interleukin-12/23 Monoclonal Antibody, in Patients With Moderate-to-Severe Crohn's Disease

CLINICAL–ALIMENTARY TRACT

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See Maser EA et al on page 1112 in *CGH*.

Background & Aims: **Interleukin-12 and interleukin-23 are inflammatory cytokines implicated in Crohn's disease pathophysiology. Ustekinumab is a monoclonal antibody against the p40 subunit of interleukin-12/23.** ***Methods:*** **We performed a double-blind, cross-over trial of the clinical effects of ustekinumab in 104 patients with moderate-to-severe Crohn's disease (population 1). Patients were given subcutaneous placebo at weeks 0–3, then ustekinumab at weeks 8–11; subcutaneous ustekinumab at weeks 0–3, then placebo at weeks 8–11; intravenous placebo at week 0, then ustekinumab at week 8; or intravenous ustekinumab at week 0, then placebo at week 8. Furthermore, an open-label trial evaluated the effects of 4 weekly subcutaneous injections or 1 intravenous infusion of ustekinumab in 27 patients who were primary or secondary nonresponders to infliximab (population 2).** ***Results:*** **In population 1, clinical response rates for the combined groups given ustekinumab and placebo were 53% and 30% ($P = .02$), respectively at weeks 4 and 6, and 49% and 40% ($P = .34$), respectively at week 8. In a subgroup of 49 patients who were previously given infliximab (neither primary nor secondary nonresponders), clinical response to ustekinumab was significantly greater than the group given placebo ($P < .05$) through week 8. In population 2, the clinical responses at week 8 to subcutaneous and intravenous ustekinumab were 43% and 54%, respectively. There was no increase in the number of adverse or serious adverse events in patients given ustekinumab through week 8 compared with placebo.** ***Conclusions:*** **Ustekinumab induced a clinical response in patients with moderate-to-severe Crohn's disease, especially in patients previously given infliximab.**

Conventional therapy for moderate-to-severe Crohn's disease includes corticosteroids and immunosuppressive therapy with azathioprine, 6-mercaptopurine, or methotrexate.[1,2] Patients who fail to respond to conventional therapies are treated with anti–tumor necrosis factor (TNF) antibodies.[1,2] Approximately one third of anti-TNF–naive patients experience primary nonresponse to anti-TNF therapy.[3–8] Of initial anti-TNF therapy responders, an additional one third subsequently lose response or become intolerant (secondary nonresponse),[4,6,8] requiring dose escalation or switching to another anti-TNF agent.[9,10] Anti-TNF therapy response rates among secondary nonresponders who switch within the class are generally lower than those among anti-TNF–naive patients.[6,8,10] Additional therapeutic options with novel mechanisms of action are needed for moderate-to-severe Crohn's disease, particularly for patients who fail anti-TNF agents.

Interleukin-12 and interleukin-23 have been implicated in the pathophysiology of Crohn's disease,[11,12] and a recent genome-wide association study found a significant association between Crohn's disease and a gene that encodes a subunit of the receptor for interleukin-23.[13] Naive $CD4^+$ T cells differentiate into 4 subsets: T-helper 1 (Th1), Th2, Th17 ($Th_{interleukin\text{-}17}$), and regulatory T cells. Interleukin-12, a heterodimer of p40 and p35 subunits, induces differentiation of naive $CD4^+$ T cells into Th1 cells,[14] which produce interferon-γ and mediate cellular immunity. Interleukin-23, a heterodimer of the same p40 subunit and a p19 subunit, induces differentiation of naive $CD4^+$ T cells into $Th_{interleukin\text{-}17}$ cells,[15,16] which produce interleukin-17, interleukin-17F, interleukin-6, and TNFα to mediate cellular immunity.

Monoclonal antibody neutralization of interleukin-12/23 via the shared p40 subunit is effective in treating animal models of colitis.[17–20] Furthermore, a human immunoglobulin (Ig)G1 monoclonal antibody to the interleukin-12/23 p40 subunit, ABT-874 (J695), was reported to possibly induce clinical response and remission in a

Abbreviations used in this paper: Th cell, T-helper cell; TNF, tumor necrosis factor.

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phase 2 study of patients with active Crohn's disease.[21] Further research is needed to elucidate the role of interleukin-12 and interleukin-23 in other pathogenic disease processes and to determine whether the common p40 subunit has biologic activities that are separate and distinct from the p35 and p19 subunits of the respective cytokines either as heterodimers or monomers.

Ustekinumab is a fully human IgG1 monoclonal antibody that targets the interleukin 12/23 shared p40 subunit. Anti–interleukin-12/23 therapy with ustekinumab has shown efficacy in psoriasis[22–24] and has been evaluated in multiple sclerosis.[25] Here we report the results of a randomized, placebo-controlled, phase 2a induction trial of ustekinumab in patients with moderate-to-severe Crohn's disease.

Materials and Methods

Patients

This trial was conducted between May 2004 and October 2006. The protocol was approved by the institutional review board at each center. All patients gave written informed consent.

Eligible patients were adults with moderate-to-severe Crohn's disease of at least 6 weeks' duration and a Crohn's disease activity index (CDAI) score of 220–450 points (range, 0–600 points; greater scores indicate more severe disease).[26] Crohn's colitis, ileitis, or ileocolitis was confirmed by radiography or endoscopy. Ineligible patients were those testing positive for a tuberculin skin test and patients with short-bowel syndrome, an ostomy, obstructive symptoms with strictures, current or recent opportunistic infection or abscess, cancer, recent treatment with any investigational agent or an anti-TNF agent including infliximab within the past 16 weeks.

Concomitant use of 5-aminosalicylates, antibiotics, prednisolone at a maximum daily dose of 20 mg, azathioprine, 6-mercaptopurine, or methotrexate was permitted. Concomitant medication doses remained constant, except corticosteroids, which could be tapered by 2.5 mg/wk after week 8.

Two populations were studied. Population 1 had received at least one of the following: 5-aminosalicylates, antibiotics, corticosteroids, azathioprine, 6-mercaptopurine, or methotrexate; submaximal infliximab doses or regimens (ie, only 1–2 induction doses of infliximab 5 mg/kg, or maintenance doses of infliximab 5 mg/kg every 8 weeks without shortening the dosing interval or escalating to infliximab 10 mg/kg, or infliximab intolerance); or other anti-TNFα agents. Population 2 comprised nonresponders to a 3-dose induction of infliximab 5 mg/kg (primary nonresponders) or initial responders who lost response during every-8-week maintenance therapy, despite dose escalation to 10 mg/kg (secondary nonresponders), as determined by the investigator.

Study Design

Population 1. This was a double-blind, placebo-controlled, parallel-group, cross-over study. Cross-over to the alternate therapy occurred at week 8. Patients were randomly assigned (1:1:1:1) to 1 of 4 groups: subcutaneous placebo at weeks 0, 1, 2, and 3, then 90 mg ustekinumab at weeks 8, 9, 10, and 11; subcutaneous 90 mg ustekinumab at weeks 0, 1, 2, and 3, then placebo at weeks 8, 9, 10, and 11; intravenous placebo at week 0, then 4.5 mg/kg ustekinumab at week 8; or intravenous 4.5 mg/kg ustekinumab at week 0, then placebo at week 8.

Population 2. This was an open-label study. Patients were assigned randomly (1:1) to either subcutaneous 90 mg ustekinumab at weeks 0, 1, 2, and 3, or intravenous 4.5 mg/kg ustekinumab at week 0. No additional treatment was administered at week 8.

Randomization in both study populations was performed centrally using an adaptive randomization procedure that was stratified by investigative site. Clinical response was defined as a reduction of at least 25% and 70 points in the CDAI score from week 0.[4,27] Clinical remission was defined as an absolute CDAI score of less than 150 points, and 100-point response was defined as a reduction of at least 100 points from week 0 in the CDAI score.[26,27]

Safety and Efficacy Evaluations

Patients in both populations were followed up for safety and efficacy through week 28. Data for CDAI scores were collected from patient diaries; clinical assessments, adverse events, and concomitant medications were recorded; and laboratory tests, including assessment of the C-reactive protein concentration, were performed throughout the study. Blood samples were drawn at weeks 0, 16, 28, and 54 for assessment of antibodies to ustekinumab using an antigen-bridging enzyme immunoassay.

Statistical Methods

The primary end point was clinical response at week 8 in population 1, defined as a reduction of 25% or more and 70 points or more from the baseline CDAI score. Secondary end points included clinical response at weeks 4 and 6, and clinical remission and 100-point response at weeks 4, 6, and 8. Other end points included clinical response, 100-point response, and clinical remission at week 16, a time point 8 weeks after the first dose of ustekinumab in patients who initially had been assigned to placebo from week 0 through week 8.

Patients who had a prohibited change in their concomitant Crohn's disease medication, a Crohn's disease–related surgery, or who discontinued study medication for lack of therapeutic effect were considered not to have achieved clinical response, clinical remission, or 100-point response from the time of event onward. Patients with

insufficient data to calculate their CDAI score were considered not to have achieved clinical response, clinical remission, or 100-point response at that time point. The intent-to-treat population included all randomized patients.

Comparisons between the placebo (subcutaneous and intravenous combined) and ustekinumab (subcutaneous and intravenous combined) groups were made for each end point using a 2-sided, 0.05-level Cochran–Mantel–Haenszel chi-square test, stratified by route of administration. Comparisons of each end point through week 8 by route of administration were made between placebo and ustekinumab using a 2-sided, 0.05-level Fisher's exact test.

Prespecified subgroup analyses were as follows: baseline bodyweight (<60 kg, ≥60 to <75 kg, or ≥75 kg); Crohn's disease duration (≤5 y, >5 to ≤15 y, or >15 y); C-reactive protein (<0.6 mg/dL or ≥0.6 mg/dL); and previous use (yes, no) or concomitant use (yes, no) of corticosteroids, 5-aminosalicylate compounds, azathioprine, 6-mercaptopurine, methotrexate, anti-TNF agents, or antibiotics. Odds ratios and corresponding 95% confidence intervals were determined to compare the proportion of patients in clinical response at week 8 in the combined ustekinumab and combined placebo groups.

Summaries of adverse events and antibodies to ustekinumab were based on data for all patients who received at least one dose of study medication and were based on the actual treatment received.

Sample Size

For the primary end point of clinical response at week 8 in population 1, we planned to recruit 25 patients each into the subcutaneous and intravenous ustekinumab and placebo groups, yielding a total sample size of 100 patients. Combining the subcutaneous and intravenous routes of administration for both the ustekinumab and placebo groups, 100 patients would provide 82% power to detect a difference in clinical response rates of 30% assuming a 70% rate of clinical response for ustekinumab and a 40% rate of clinical response for placebo. No power calculations were performed for population 2.

Role of the Funding Source

The steering committee of academic investigators and Centocor contributors designed this study. Centocor bioanalytic staff created the clinical database and performed the statistical analyses. All authors interpreted the data, and prepared and approved the report for submission.

Results

Patients

A total of 202 patients were enrolled, of whom 104 and 27 were randomized to treatment in populations 1 and 2, respectively, at 49 centers (Figure 1). Among the 71

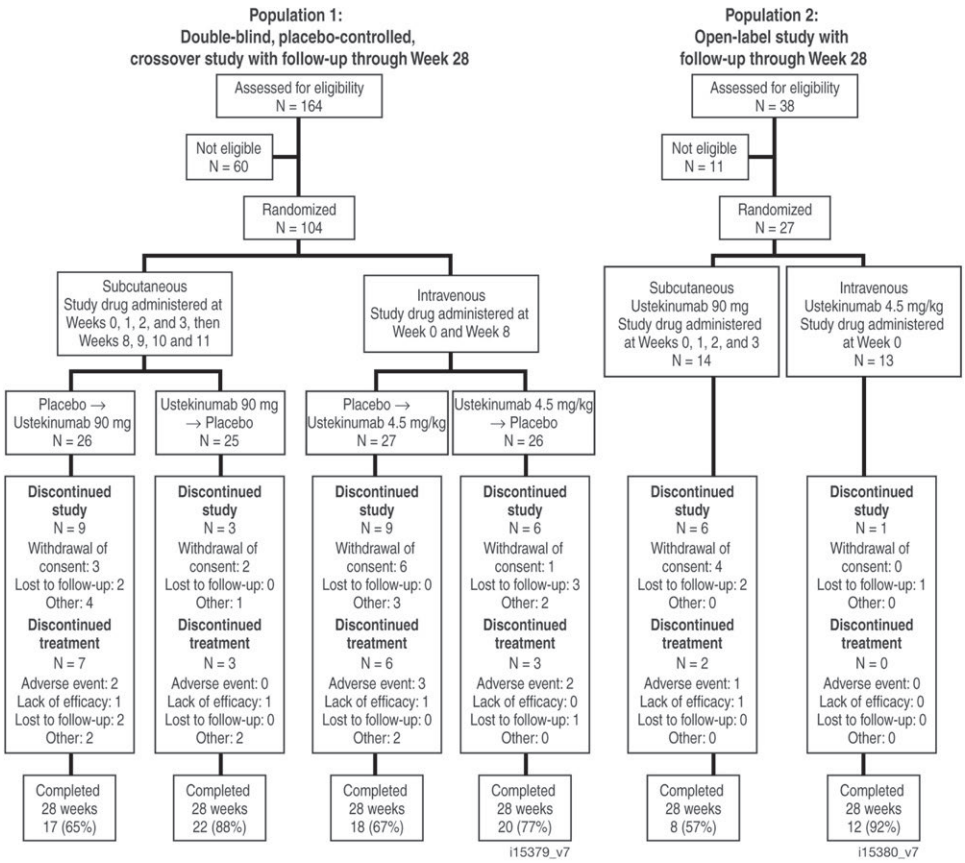

Figure 1. Efficacy and safety evaluations included 104 patients in population 1 and 27 patients in population 2.

patients enrolled but not randomized to treatment, most of these patients did not participate primarily because either screening criteria were not met (49 patients) or consent was withdrawn before randomization (9 patients).

Baseline characteristics generally were similar across treatment groups in populations 1 and 2 (Table 1). Forty-seven percent (49 of 104) of patients in population 1 and all patients (27 of 27) in population 2 received and discontinued infliximab previously. Baseline demographics and disease characteristics for patients in population 1 who previously received infliximab were similar to those for all patients in population 1 (Table 2). A greater proportion of all patients in population 1 were receiving baseline aminosalicylates compared with the subgroup of those who previously received infliximab (46 of 104 patients [44%] vs 14 of 49 patients [29%]); concomitant use of other Crohn's disease medications were comparable.

Efficacy Through Week 8

Population 1. At week 8 (the primary end point), 49% of patients in the combined ustekinumab group (25 of 51) were in clinical response compared with 40% of patients in the combined placebo group (21 of 53) (P = .34; Table 3; Figure 2*A*). At weeks 4 and 6, 53% of patients in the combined ustekinumab group (27 of 51) were in clinical response compared with 30% of patients in the combined placebo group (16 of 53) (P = .02 and .019, respectively; Table 3; Figure 2*A*). In a subgroup of 49 patients treated previously with infliximab, the rates of clinical response to ustekinumab were greater than those for placebo ($P < .05$) at every visit through week 8 (Figure 2*B*).

Through week 8, rates of clinical response, 100-point response, and clinical remission were similar for ustekinumab administered intravenously or subcutaneously; however, response rates were lower when placebo was administered intravenously rather than subcutaneously. Thus, the treatment effect (ie, difference between ustekinumab and placebo) tended to be numerically greater for intravenous compared with subcutaneous administration (Table 3).

Table 1. Patient Baseline Characteristics

	Population 1					Population 2		
Characteristic	Placebo → subcutaneous ustekinumab 90 mg (n = 26)	Subcutaneous ustekinumab 90 mg → placebo (n = 25)	Placebo → intravenous ustekinumab 4.5 mg/kg (n = 27)	Intravenous ustekinumab 4.5 mg/kg → placebo (n = 26)	Total (N = 104)	Subcutaneous ustekinumab 90 mg (n = 14)	Intravenous ustekinumab 4.5 mg/kg (n = 13)	Total (N = 27)
Male sex	15 (58%)	15 (60%)	13 (48%)	14 (54%)	57 (55%)	8 (57%)	5 (39%)	13 (48%)
Mean age ± SD, y	37 ± 14	37 ± 13	44 ± 11	43 ± 12	40 ± 13	47 ± 14	43 ± 11	45 ± 13
Mean weight ± SD, kg	76 ± 18	73 ± 16	83 ± 27	78 ± 24	78 ± 22	75 ± 18	71 ± 20	73 ± 19
Mean duration of disease ± SD, y	13 ± 11	12 ± 10	11 ± 9	13 ± 13	12 ± 11	13 ± 11	13 ± 9	13 ± 10
Disease site								
Ileum	21 (81%)	18 (72%)	19 (70%)	22 (85%)	80 (77%)	7 (50%)	7 (54%)	14 (52%)
Colon	14 (54%)	17 (68%)	20 (74%)	11 (42%)	62 (60%)	10 (71%)	11 (85%)	21 (78%)
Proximal GI tract	1 (4%)	4 (16%)	2 (7%)	0 (0%)	7 (7%)	0 (0%)	0 (0%)	0 (0%)
Previous surgery	9 (35%)	3 (12%)	10 (37%)	11 (42%)	33 (32%)	6 (43%)	4 (31%)	10 (37%)
CDAI score[a]	292 ± 40	311 ± 80	316 ± 56	325 ± 66	311 ± 62	314 ± 69	333 ± 67	323 ± 68
C-reactive protein level, mg/dL[b]								
n	25	25	26	26	102	14	13	27
Mean ± SD	1.2 ± 1.4	1.7 ± 2.3	1.3 ± 1.3	1.3 ± 2.1	1.4 ± 1.8	1.8 ± 2.3	2.2 ± 3.6	2.0 ± 2.9
Median	0.6	0.9	0.7	0.6	0.7	0.75	1.10	1.00
Range	0.2–4.8	0.2–9.6	0.2–4.2	0.2–8.9	0.2–9.6	0.2–8.4	0.2–13.8	0.2–13.8
Concomitant medications	21 (81%)	19 (76%)	19 (70%)	20 (77%)	79 (76%)	10 (71%)	11 (85%)	21 (78%)
Oral cortico-steroids	8 (31%)	10 (40%)	8 (30%)	7 (27%)	33 (32%)	6 (43%)	4 (31%)	10 (37%)
≤20 mg/day	7 (27%)	9 (36%)	6 (22%)	5 (19%)	27 (26%)	4 (29%)	1 (8%)	5 (19%)
>20 mg/day	1 (4%)	1 (4%)	2 (7%)	2 (8%)	6 (6%)	2 (14%)	3 (23%)	5 (19%)
Immunosuppressants	10 (39%)	5 (20%)	10 (37%)	10 (39%)	35 (34%)	6 (43%)	8 (62%)	14 (52%)
6-MP, AZA	7 (27%)	4 (16%)	8 (30%)	9 (35%)	28 (27%)	4 (29%)	8 (62%)	12 (44%)
Methotrexate	3 (12%)	1 (4%)	2 (7%)	1 (4%)	7 (7%)	2 (14%)	0 (0%)	2 (7%)
Antibiotics	2 (8%)	2 (8%)	2 (7%)	1 (4%)	7 (7%)	2 (14%)	1 (8%)	3 (11%)
Aminosalicylates	13 (50%)	9 (36%)	14 (52%)	10 (39%)	46 (44%)	7 (50%)	5 (39%)	12 (44%)
Oral corticosteroids or immunosuppressants	14 (54%)	13 (52%)	14 (52%)	15 (58%)	56 (54%)	9 (64%)	8 (62%)	17 (63%)
Oral corticosteroids and immunosuppressants	4 (15%)	2 (8%)	4 (15%)	2 (8%)	12 (12%)	3 (21%)	4 (31%)	7 (26%)
Prior infliximab exposure[c]	16 (62%)	14 (56%)	11 (41%)	8 (31%)	49 (47%)	14 (100%)	13 (100%)	27 (100%)
Failed to respond to induction	NA	NA	NA	NA	NA	5 (36%)	5 (39%)	10 (37%)
Lost response and did not regain response	NA	NA	NA	NA	NA	9 (64%)	8 (62%)	17 (63%)
Current smoker, n	7 (27%)	10 (40%)	8 (30%)	13 (50%)	38 (37%)	3 (21%)	5 (39%)	8 (30%)

AZA, azathioprine; GI, gastrointestinal; 6-MP, 6-mercaptopurine; NA, not applicable.
[a]Scores for the CDAI can range from 0–600; higher scores indicate more severe disease activity.
[b]The normal range is 0.6 mg/dL or less.
[c]These patients did not receive infliximab 16 weeks before baseline.

Table 2. Baseline Characteristics for Patients who Previously Received Infliximab: Population 1

Characteristic	Placebo → subcutaneous ustekinumab 90 mg (n = 16)	Subcutaneous ustekinumab 90 mg → placebo (n = 14)	Placebo → intravenous ustekinumab 4.5 mg/kg (n = 11)	Intravenous ustekinumab 4.5 mg/kg → placebo (n = 8)	Total (N = 49)
Male sex	9 (56%)	7 (50%)	4 (36%)	3 (38%)	23 (47%)
Mean age ± SD, y	37 ± 13	37 ± 12	39 ± 10	42 ± 8	38 ± 11
Mean weight ± SD, kg	75 ± 19	70 ± 19	78 ± 27	69 ± 18	73 ± 20
Mean duration of disease ± SD, y	12 ± 7	15 ± 12	14 ± 9	16 ± 9	14 ± 9
Disease site					
Ileum	13 (81%)	11 (79%)	9 (82%)	8 (100%)	41 (84%)
Colon	10 (63%)	11 (79%)	7 (64%)	2 (25%)	30 (61%)
Proximal GI tract	0 (0.0%)	2 (14%)	1 (9%)	0 (0%)	3 (6%)
Previous surgery	6 (38%)	3 (21%)	5 (45%)	6 (75%)	20 (41%)
CDAI score[a]	302 ± 46	337 ± 62	307 ± 56	358 ± 62	322 ± 58
C-reactive protein level, mg/dL[b]					
n	16	14	11	8	49
Mean ± SD	1.1 ± 1.5	1.8 ± 1.9	1.2 ± 1.4	0.8 ± 0.8	1.3 ± 1.5
Median	0.6	1.1	0.4	0.7	0.7
Range	(0.2–4.8)	(0.2–6.2)	(0.2–4.2)	(0.2–2.8)	(0.2–6.2)
Concomitant medications	12 (75%)	10 (71%)	7 (64%)	6 (75%)	35 (71%)
Oral corticosteroids	5 (31%)	6 (43%)	3 (27%)	3 (38%)	17 (35%)
≤20 mg/day	4 (25%)	5 (36%)	3 (27%)	1 (13%)	13 (27%)
>20 mg/day	1 (6%)	1 (7%)	0 (0%)	2 (25%)	4 (8%)
Immunosuppressants	8 (50%)	3 (21%)	5 (46%)	4 (50%)	20 (41%)
6-MP, AZA	5 (31%)	2 (14%)	3 (27%)	4 (50%)	14 (29%)
Methotrexate	3 (19%)	1 (7%)	2 (18%)	0 (0%)	6 (12%)
Antibiotics	1 (6%)	1 (7%)	2 (18%)	1 (13%)	5 (10%)
Aminosalicylates	6 (38%)	3 (21%)	3 (27%)	2 (25%)	14 (29%)
Oral corticosteroids or immunosuppressants	10 (63%)	9 (64%)	6 (55%)	5 (63%)	30 (61%)
Oral corticosteroids and immunosuppressants	3 (19%)	0 (0%)	2 (18%)	2 (25%)	7 (14%)
Current smoker, n	6 (38%)	5 (36%)	4 (36%)	5 (63%)	20 (41%)

NOTE. These patients did not receive infliximab 16 weeks before baseline.
AZA, azathioprine; GI, gastrointestinal; 6-MP, 6-mercaptopurine.
[a]Scores for the CDAI can range from 0–600; higher scores indicate more severe disease activity.
[b]The normal range is 0.6 mg/dL or less.

The odds ratio and 95% confidence intervals for comparing the proportion of patients in clinical response at week 8 in the combined ustekinumab and placebo groups by subgroups of baseline weight, disease characteristics, and Crohn's disease medication history are shown in Figure 2*C*. Lower baseline body weight and higher baseline CDAI scores both were associated with a higher rate of clinical response to ustekinumab at week 8.

Although formal statistical testing was not performed, the median C-reactive protein concentrations were numerically unchanged or increased at week 8 compared with baseline in patients who initially received intravenous or subcutaneous placebo, whereas these values were decreased at week 8 in patients who initially received intravenous or subcutaneous ustekinumab (Figure 2*D*).

Population 2. The rates of clinical response, 100-point response, and clinical remission through week 8 in the combined and individual intravenous and subcutaneous ustekinumab groups are shown in Table 3. Clinical response rates for patients in the combined ustekinumab group were 22% (6 of 27) and 41% (11 of 27) at weeks 2 and 4, respectively. At weeks 6 and 8, 48% of patients in the combined ustekinumab group (13 of 27) were in clinical response. In general, numerically higher rates of clinical response, 100-point response, and clinical remission were observed in the intravenous ustekinumab group than in the subcutaneous ustekinumab group. Median C-reactive protein concentrations were decreased at week 8 compared with baseline in the subcutaneous (0.75 vs 0.6 mg/dL) and intravenous (1.1 vs 0.6 mg/dL) ustekinumab groups.

Efficacy at Week 16

Efficacy results at week 16 (ie, 8 weeks after treatment cross-over) in population 1 are presented by randomized treatment group in Table 4. Given the long median half-life of ustekinumab (20–39 days),[25] high

Table 3. Primary and Secondary Efficacy Results Through Week 8

	Population 1						Population 2		
	Subcutaneous		Intravenous		Combined		Subcutaneous	Intravenous	Combined
	Placebo (n = 26)	Ustekinumab 90 mg (n = 25)	Placebo (n = 27)	Ustekinumab 4.5 mg/kg (n = 26)	Placebo (N = 53)	Ustekinumab (N = 51)	Ustekinumab 90 mg (n = 14)	Ustekinumab 4.5 mg/kg (n = 13)	Ustekinumab (N = 27)
Clinical response[a]									
Week 2	11 (42%)	11 (44%)	6 (22%)	10 (39%)	17 (32%)	21 (41%)	1 (7%)	5 (39%)	6 (22%)
P value[b,c]		1.00		.241		.335			
Week 4	8 (31%)	13 (52%)	8 (30%)	14 (54%)	16 (30%)	27 (53%)	3 (21%)	8 (62%)	11 (41%)
P value[b,c]		.160		.098		.02			
Week 6	10 (39%)	13 (52%)	6 (22%)	14 (54%)	16 (30%)	27 (53%)	5 (36%)	8 (62%)	13 (48%)
P value[b,c]		.404		.024		.019			
Week 8	13 (50%)	12 (48%)	8 (30%)	13 (50%)	21 (40%)	25 (49%)	6 (43%)	7 (54%)	13 (48%)
P value[b,c]		1.000		.166		.337			
100-point response[a]									
Week 2	6 (23%)	9 (36%)	6 (22%)	8 (31%)	12 (23%)	17 (33%)	0 (0%)	5 (39%)	5 (19%)
P value[c]						.228			
Week 4	7 (27%)	11 (44%)	7 (26%)	11 (42%)	14 (26%)	22 (43%)	2 (14%)	6 (46%)	8 (30%)
P value[c]						.076			
Week 6	9 (35%)	12 (48%)	4 (15%)	13 (50%)	13 (25%)	25 (49%)	4 (29%)	7 (54%)	11 (41%)
P value[c]						.010			
Week 8	9 (35%)	12 (48%)	7 (26%)	13 (50%)	16 (30%)	25 (49%)	5 (36%)	5 (39%)	10 (37%)
P value[c]						.052			
Clinical remission[a]									
Week 2	3 (12%)	6 (24%)	2 (7%)	5 (19%)	5 (9%)	11 (22%)	0 (0%)	1 (8%)	1 (4%)
P value[c]						.089			
Week 4	4 (15%)	6 (24%)	4 (15%)	7 (27%)	8 (15%)	13 (26%)	1 (7%)	3 (23%)	4 (15%)
P value[c]						.191			
Week 6	6 (23%)	7 (28%)	3 (11%)	6 (23%)	9 (17%)	13 (26%)	2 (14%)	4 (31%)	6 (22%)
P value[c]						.290			
Week 8	6 (23%)	6 (24%)	3 (11%)	7 (27%)	9 (17%)	13 (26%)	3 (21%)	4 (31%)	7 (26%)
P value[c]						.292			

[a]Patients who discontinued the study agent because of an unsatisfactory therapeutic effect, had insufficient data to assess their response/remission status, had prohibited Crohn's disease–related surgery, or had prohibited concomitant medication changes were considered not in clinical response, remission, or to not have achieved a 100-point response, regardless of their CDAI score.
[b]*P* values for the comparison between the subcutaneous placebo and subcutaneous ustekinumab groups and between the intravenous placebo and intravenous ustekinumab groups were performed using a 2-sided Fisher's exact test. *P* values are shown for the end points analyzed.
[c]*P* values for the comparison between the combined placebo and combined ustekinumab groups were performed using a 2-sided Cochran–Mantel–Haenszel chi-square test stratified by route of administration. *P* values are shown for the end points analyzed.

placebo response rate at earlier time points, and a potential carryover effect, cross-over efficacy results of ustekinumab at week 16 are difficult to interpret. Efficacy results at week 16 for the intravenous and subcutaneous ustekinumab groups in population 2 also are presented in Table 4.

Safety

Adverse events through week 8 in population 1 (placebo-controlled). The proportions of patients with one or more adverse events and patients who discontinued treatment because of an adverse event were slightly higher in the combined placebo group than in the combined ustekinumab group (Table 5). Specifically, the incidence of nausea, worsening Crohn's disease, and fatigue were slightly higher in patients in the placebo group and the incidence of pruritus and anxiety were slightly higher in patients in the ustekinumab group (Table 5). The frequencies of other adverse events through week 8 generally were similar in the 2 groups (Table 5).

Three patients (6%) in the placebo group experienced one or more serious adverse events (small intestinal stenosis and nonsteroidal anti-inflammatory drug-induced gastrointestinal ulceration, worsening Crohn's disease and erythema nodosum, worsening Crohn's disease and small intestinal obstruction). Two patients (4%) in the ustekinumab group experienced one or more serious adverse events (small intestinal obstruction and coronary artery disease).

Twelve patients (23%) in the placebo group experienced one or more infections as compared with 8 patients (15%) in the ustekinumab group (Table 5). No

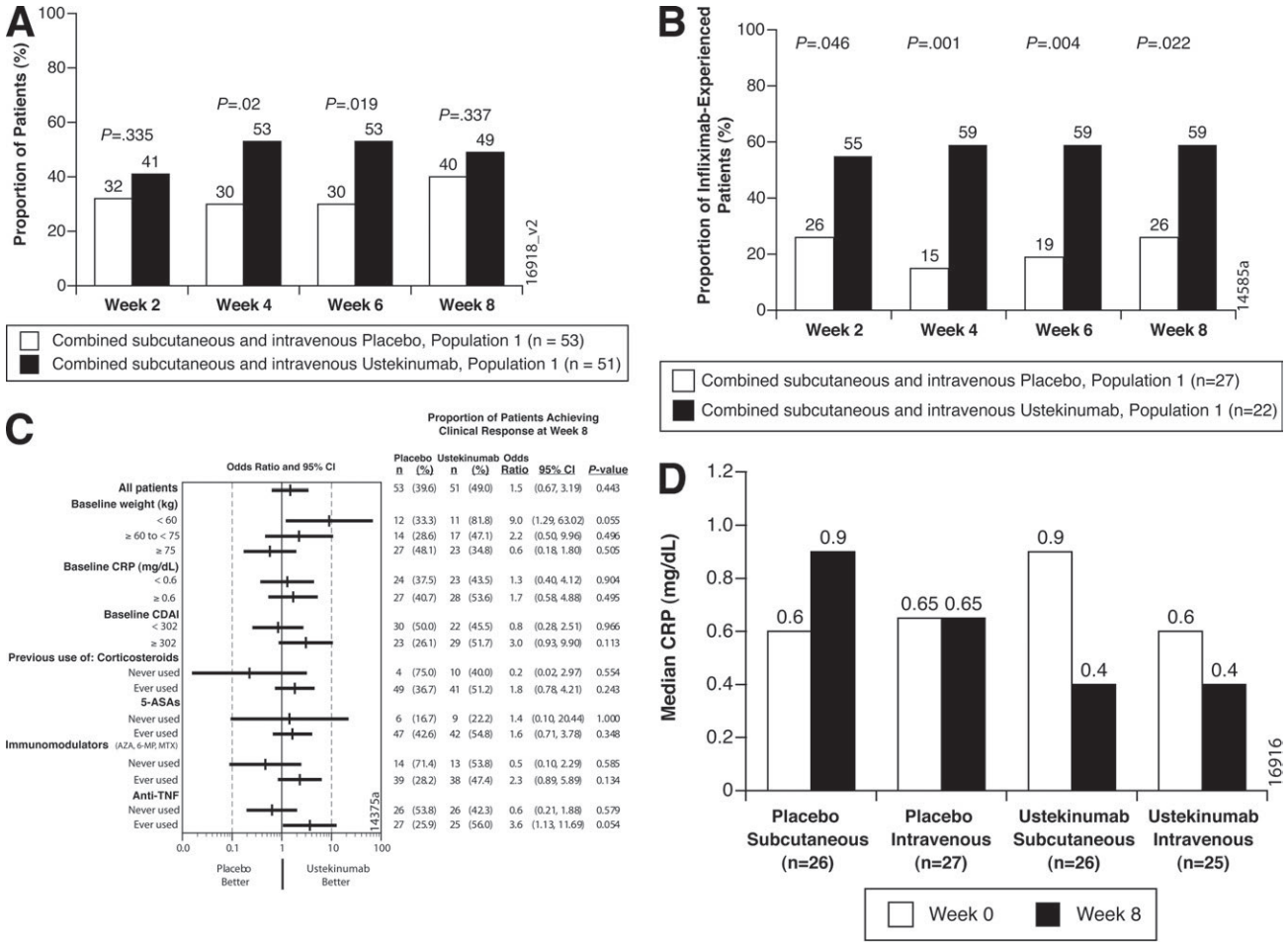

Figure 2. Efficacy of ustekinumab. (*A*) Clinical response over time in the combined ustekinumab and placebo groups in population 1. (*B*) Clinical response over time in the combined ustekinumab and placebo groups in Population 1 who previously had been treated with infliximab. (*C*) Odds ratio and 95% confidence intervals for comparing the proportion of patients in clinical response at week 8 in the combined ustekinumab or placebo groups in population 1 stratified by baseline weight, disease characteristics, and Crohn's disease medication history. (*D*) Median C-reactive protein (CRP) concentrations at week 0 and week 8 in patients treated with subcutaneous or intravenous ustekinumab or placebo in population 1.

patients in either group experienced serious infections, opportunistic infections, or malignancy.

Administration site reactions (eg, injection site irritation or discomfort) generally were mild and occurred more commonly in patients treated with subcutaneous placebo (4%) than subcutaneous ustekinumab (0%), whereas adverse events occurring within 1 hour of intravenous administration (eg, pyrexia, flushing, and pruritus) generally were mild and occurred more frequently for patients treated with intravenous ustekinumab (19%) than intravenous placebo (0%) (Table 5).

Adverse events after initial ustekinumab dose through week 28 in populations 1 and 2. The proportions of patients with one or more adverse events and patients who discontinued treatment because of an adverse event are shown in Table 6. Six patients (6%) in population 1 experienced one or more serious adverse events (worsening Crohn's disease [n = 2], colonic stenosis and pneumothorax [n = 1], small intestinal obstruction [n = 2], and prostate cancer [n = 1, see later] in a patient who had coronary artery disease in the placebo-controlled period). Four patients (15%) in population 2 experienced one or more serious adverse events (viral gastroenteritis [n = 1, see later]; nephrolithiasis [n = 1]; worsening Crohn's disease [n = 1]; worsening Crohn's disease, syncope, and disseminated histoplasmosis [n = 1, see later]).

Two patients in population 2 developed serious infections. Disseminated histoplasmosis occurred in a patient who discontinued infliximab 10 mg/kg 3 months before study entry, was febrile at baseline, and received intravenous ustekinumab, azathioprine, and prednisone concomitantly during the study. Viral gastroenteritis occurred in 1 patient who received subcutaneous ustekinumab.

Two patients in population 1 developed malignancies. A 54-year-old man with increased prostate-specific antigen levels before study entry was diagnosed with prostate carcinoma 2 months after receiving intravenous usteki-

Table 4. Efficacy Results at Weeks 12, 14, and 16

	Population 1[a]				Population 2	
	Placebo → subcutaneous ustekinumab 90 mg (n = 26)	Subcutaneous ustekinumab 90 mg → placebo (n = 25)	Placebo → intravenous ustekinumab 4.5 mg/kg (n = 27)	Intravenous ustekinumab 4.5 mg/kg → placebo (n = 26)	Subcutaneous ustekinumab 90 mg (n = 14)	Intravenous ustekinumab 4.5 mg/kg (n = 13)
Clinical response[b]	8 (31%)	10 (40%)	7 (26%)	10 (39%)	3 (21%)	6 (46%)
Week 12	12 (46%)	12 (48%)	7 (26%)	12 (46%)	5 (36%)	8 (62%)
Week 14	9 (35%)	12 (48%)	7 (26%)	9 (35%)	5 (36%)	8 (62%)
Week 16	8 (31%)	10 (40%)	7 (26%)	10 (39%)	3 (21%)	6 (46%)
100-point response[b]	8 (31%)	9 (36%)	6 (22%)	9 (35%)	3 (21%)	6 (46%)
Week 12	10 (39%)	12 (48%)	6 (22%)	8 (31%)	5 (36%)	8 (62%)
Week 14	8 (31%)	10 (40%)	7 (26%)	8 (31%)	4 (29%)	8 (62%)
Week 16	8 (31%)	9 (36%)	6 (22%)	9 (35%)	3 (21%)	6 (46%)
Clinical remission[b]	6 (23%)	5 (20%)	4 (15%)	6 (23%)	2 (14%)	0 (0%)
Week 12	8 (31%)	6 (24%)	3 (11%)	6 (23%)	3 (21%)	4 (31%)
Week 14	6 (23%)	6 (24%)	4 (15%)	7 (27%)	2 (14%)	3 (23%)
Week 16	6 (23%)	5 (20%)	4 (15%)	6 (23%)	2 (14%)	0 (0%)

[a]Population 1, weeks 12, 14, and 16 clinical response, 100-point clinical response, and clinical remission represent the clinical end point results 8 weeks after crossover to the alternate study medication.
[b]Patients who discontinued the study agent because of an unsatisfactory therapeutic effect, had insufficient data to assess their response/remission status, had prohibited Crohn's disease–related surgery, or had prohibited concomitant medication changes were considered not in clinical response, remission, or to not have achieved a 100-point response, regardless of their CDAI score.

numab. Squamous and basal cell skin carcinomas were diagnosed after week 28 (approximately 6 months after the last ustekinumab dose) in a woman treated with subcutaneous ustekinumab starting at week 8.

Anti-ustekinumab antibodies. Of the 77 patients in population 1 and 22 patients in population 2 who had serum samples available for the assessment of anti-ustekinumab antibodies, none (0%) was positive at any time through week 54. In population 1, 25% (19 of 77) of patients had undetectable anti-ustekinumab antibodies owing to detectable serum ustekinumab levels, and 75% (58 of 77) of patients were negative for anti-ustekinumab antibodies. Similarly, in population 2, 23% (5 of 22) of patients had undetectable anti-ustekinumab antibodies and 77% (17 of 22) of patients were negative for anti-ustekinumab antibodies.

Discussion

Induction of response and remission in patients with active Crohn's disease who fail to respond to conventional therapy (including anti-TNF therapy) is an important unmet clinical need. Inhibition of the interleukin-12/23 inflammation pathways via monoclonal antibody blockade of their common p40 subunit constitutes a unique mechanism of action for Crohn's disease therapy. Although the results of this phase 2, exploratory trial failed to definitively show that induction therapy with ustekinumab was superior to placebo in patients with moderate-to-severe Crohn's disease, the data generally are consistent with a beneficial treatment effect.

In population 1, the primary end point was not achieved. Clinical response rates at week 8 were 49% and 40% for the combined intravenous and subcutaneous ustekinumab and the combined intravenous and subcutaneous placebo groups, respectively ($P = .34$). Differences were observed between the combined ustekinumab and combined placebo groups at weeks 4 and 6 ($P < .05$) primarily owing to lower placebo response rates. Differences also were observed in patients treated previously with infliximab ($P < .05$) and in patients who had high baseline CDAI scores. Ustekinumab therapy in populations 1 and 2 also numerically reduced median baseline C-reactive protein concentrations whereas placebo treatment in population 1 did not. These data generally are similar to those of a phase 2 study of patients with active Crohn's disease in which another interleukin-12/23 p40 subunit monoclonal antibody, ABT-874 (J695), possibly induced clinical response and remission.[21]

The high placebo-response rate at week 8 may have limited our ability to detect a treatment benefit.[28–30] A meta-analysis of trial design features and patient demographic characteristics associated with higher rates of placebo response in induction trials conducted in patients with active Crohn's disease showed that disease activity at entry (CDAI score <200 points), study visit frequency (<4-wk intervals), and study duration (>4 wk), were important predictors of the placebo remission rate, with study duration being the most important independent predictor.[31] Defining clinical response as a reduction from baseline in CDAI score of 100 points or more, provides greater discrimination between active treatment and placebo.[32] By using this definition for clinical response, we found greater discrimination at week 8 between ustekinumab and placebo (49% vs 30%, respec-

Table 5. Adverse Events in Population 1 Through Week 8

	Subcutaneous		Intravenous		Combined	
	Placebo (n = 26)	Ustekinumab 90 mg (n = 25)	Placebo (n = 26)	Ustekinumab 4.5 mg/kg (n = 27)	Placebo (N = 52)	Ustekinumab (N = 52)
Total with adverse events	22 (85%)	17 (68%)	19 (73%)	20 (74%)	41 (79%)	37 (71%)
Adverse events during treatment with an incidence of ≥5%[a]						
Nausea	6 (23%)	0 (0%)	3 (12%)	1 (4%)	9 (17%)	1 (2%)
Headache	4 (15%)	4 (16%)	4 (15%)	2 (7%)	8 (15%)	6 (12%)
Abdominal pain	4 (15%)	2 (8%)	2 (8%)	4 (15%)	6 (12%)	6 (12%)
Worsening Crohn's disease	4 (15%)	1 (4%)	3 (12%)	3 (11%)	7 (14%)	4 (8%)
Fatigue	2 (8%)	0 (0%)	4 (15%)	1 (4%)	6 (12%)	1 (2%)
Upper respiratory tract infection	0 (0%)	3 (12%)	3 (12%)	1 (4%)	3 (6%)	4 (8%)
Pharyngolaryngeal pain	3 (12%)	1 (4%)	2 (8%)	1 (4%)	5 (10%)	2 (4%)
Pruritus	0 (0%)	0 (0%)	0 (0%)	3 (11%)	0 (0%)	3 (6%)
Dyspepsia	1 (4%)	2 (8%)	0 (0%)	0 (0%)	1 (2%)	2 (4%)
Flatulence	2 (8%)	1 (4%)	0 (0%)	0 (0%)	2 (4%)	1 (2%)
Vomiting	2 (8%)	1 (4%)	0 (0%)	0 (0%)	2 (4%)	1 (2%)
Upper abdominal pain	1 (4%)	0 (0%)	2 (8%)	0 (0%)	3 (6%)	0 (0%)
Abnormal bowel sounds	0 (0%)	0 (0%)	2 (8%)	0 (0%)	2 (4%)	0 (0%)
Rash	1 (4%)	1 (4%)	2 (8%)	2 (7%)	3 (6%)	3 (6%)
Nasopharyngitis	0 (0%)	2 (8%)	0 (0%)	0 (0%)	0 (0%)	2 (4%)
Pyrexia	2 (8%)	1 (4%)	1 (4%)	2 (7%)	3 (6%)	3 (6%)
Pain	2 (8%)	2 (8%)	1 (4%)	0 (0%)	3 (6%)	2 (4%)
Influenza-like illness	0 (0%)	0 (0%)	2 (8%)	1 (4%)	2 (4%)	1 (2%)
Dizziness	1 (4%)	1 (4%)	2 (8%)	1 (4%)	3 (6%)	2 (4%)
Arthralgia	1 (4%)	2 (8%)	2 (8%)	1 (4%)	3 (6%)	3 (6%)
Dyspnea	2 (8%)	1 (4%)	0 (0%)	1 (4%)	2 (4%)	2 (4%)
Cough	2 (8%)	1 (4%)	1 (4%)	0 (0%)	3 (6%)	1 (2%)
Anxiety	0 (0%)	2 (8%)	0 (0%)	1 (4%)	0 (0%)	3 (6%)
Insomnia	0 (0%)	0 (0%)	2 (8%)	1 (4%)	2 (4%)	1 (2%)
Abdominal distension	0 (0%)	0 (0%)	0 (0%)	2 (7%)	0 (0%)	2 (4%)
Adverse events leading to treatment discontinuation	2 (8%)	0 (0%)	3 (12%)	2 (8%)	5 (10%)	2 (4%)
Serious adverse events	2 (8%)	0 (0%)	1 (4%)	2 (7%)	3 (6%)	2 (4%)
Infections	5 (19%)	4 (16%)	7 (27%)	4 (15%)	12 (23%)	8 (15%)
Serious infections	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Opportunistic infections	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Malignancy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Patients with one or more administration-site reactions	2 (8%)	0 (0%)	0 (0%)	0 (0%)	2 (4%)	0 (0%)
Patients with one or more adverse events occurring ≤1 hour after study agent administration	3 (12%)	1 (4%)	0 (0%)	5 (19%)	3 (6%)	6 (12%)

[a]According to the Medical Dictionary for Regulatory Activities (MedDRA), descending total frequency.

tively; $P = .052$), than when a 25% or greater and 70-point reduction or greater was the criterion.

Among the subgroup of patients in population 1 who had been treated previously with infliximab but who did not meet a formal definition of primary or secondary infliximab failure, differences were observed between the combined ustekinumab and combined placebo groups at all time points through week 8 ($P < .05$), again primarily owing to lower placebo-response rates. These findings are consistent with induction studies with other biologic agents that have reported a lower placebo-response rate in patients treated previously with infliximab.[7,10,29] In population 2, composed of patients who had experienced primary or secondary failure to infliximab, responses to ustekinumab generally were similar to population 1. If these findings are confirmed in phase 3 trials, ustekinumab may provide an important new option for treating Crohn's disease.

In population 1, week 16 results are confounded by the subjective nature of the CDAI and the high placebo response rate seen at early time points. Patients who responded to placebo early would not be expected to have an augmented response after crossover to ustekinumab. The relapsing and remitting nature of Crohn's disease and patients' expectation that they would receive active drug at some point during the trial also could have been contributing factors to the observed response rates at week 16.

When comparing subcutaneous and intravenous routes of administration in population 1, the response to ustekinumab was similar at all time points through week 8. However, intravenous administration yielded a consistently lower placebo response rate through week 8, resulting in a numerically greater treatment effect for intravenous compared with subcutaneous administration. The reason for this route-of-administration–based placebo response-rate difference is unclear. In population 2, the proportion of combined ustekinumab patients in clinical response at week 8 generally was similar to population 1, even though these patients were relatively more

Table 6. Adverse Events After Initial Ustekinumab Dose Through Week 28

	Population 1						Population 2		
	Placebo → subcutaneous ustekinumab 90 mg (n = 22)	Subcutaneous ustekinumab 90 mg → placebo (n = 25)	Combined subcutaneous (N = 47)	Placebo → intravenous ustekinumab 4.5 mg/kg (n = 19)	Intravenous ustekinumab 4.5 mg/kg → placebo (n = 27)	Combined intravenous (N = 46)	Subcutaneous ustekinumab 90 mg (n = 14)	Intravenous ustekinumab 4.5 mg/kg (n = 13)	Combined (N = 27)
Mean duration of follow-up period, wk	17.9	25.8	22.1	19.0	24.3	22.1	22.5	26.7	24.5
Total with at least one adverse event	16 (73%)	23 (92%)	39 (83%)	17 (90%)	23 (85%)	40 (87%)	12 (86%)	10 (77%)	22 (82%)
Adverse events during treatment with an incidence of ≥10%[a]									
Worsening Crohn's disease	6 (27%)	5 (20%)	11 (23%)	5 (26%)	7 (26%)	12 (26%)	4 (29%)	5 (39%)	9 (33%)
Nausea	5 (23%)	2 (8%)	7 (15%)	2 (11%)	3 (11%)	5 (11%)	3 (21%)	2 (15%)	5 (19%)
Abdominal pain	3 (14%)	2 (8%)	5 (11%)	0 (0%)	5 (19%)	5 (11%)	2 (14%)	0 (0%)	2 (7%)
Abdominal distension	1 (5%)	2 (8%)	3 (6%)	0 (0%)	3 (11%)	3 (7%)	1 (7%)	0 (0%)	1 (4%)
Dyspepsia	2 (9%)	3 (12%)	5 (11%)	0 (0%)	1 (4%)	1 (2%)	2 (14%)	1 (8%)	3 (11%)
Upper respiratory tract infection	6 (27%)	5 (20%)	11 (23%)	3 (16%)	4 (15%)	7 (15%)	1 (7%)	3 (23%)	4 (15%)
Nasopharyngitis	1 (5%)	3 (12%)	4 (9%)	1 (5%)	1 (4%)	2 (4%)	1 (7%)	2 (15%)	3 (11%)
Influenza	0 (0%)	3 (12%)	3 (6%)	0 (0%)	2 (7%)	2 (4%)	1 (7%)	0 (0%)	1 (4%)
Viral gastroenteritis	0 (0%)	1 (4%)	1 (2%)	2 (11%)	1 (4%)	3 (7%)	0 (0%)	3 (23%)	3 (11%)
Sinusitis	1 (5%)	0 (0%)	1 (2%)	2 (11%)	1 (4%)	3 (7%)	1 (7%)	0 (0%)	1 (4%)
Urinary tract infection	0 (0%)	0 (0%)	0 (0%)	1 (5%)	1 (4%)	2 (4%)	1 (7%)	2 (15%)	3 (11%)
Headache	0 (0%)	6 (24%)	6 (13%)	3 (16%)	4 (15%)	7 (15%)	3 (21%)	3 (23%)	6 (22%)
Dizziness	1 (5%)	1 (4%)	2 (4%)	2 (11%)	1 (4%)	3 (7%)	0 (0%)	0 (0%)	0 (0%)
Migraine	3 (14%)	0 (0%)	3 (6%)	0 (0%)	1 (4%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Syncope	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (15%)	2 (7%)
Arthralgia	0 (0%)	5 (20%)	5 (11%)	3 (16%)	3 (11%)	6 (13%)	1 (7%)	2 (15%)	3 (11%)
Back pain	0 (0%)	3 (12%)	3 (6%)	0 (0%)	2 (7%)	2 (4%)	2 (14%)	1 (8%)	3 (11%)
Rash	1 (5%)	3 (12%)	4 (9%)	1 (5%)	3 (11%)	4 (9%)	0 (0%)	0 (0%)	0 (0%)
Pruritus	0 (0%)	0 (0%)	0 (0%)	1 (5%)	3 (11%)	4 (9%)	0 (0%)	1 (8%)	1 (4%)
Pyrexia	0 (0%)	4 (16%)	4 (9%)	0 (0%)	3 (11%)	3 (7%)	1 (7%)	3 (23%)	4 (15%)
Chest pain	1 (5%)	1 (4%)	2 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	2 (15%)	3 (11%)
Fatigue	1 (5%)	1 (4%)	2 (4%)	1 (5%)	2 (7%)	3 (7%)	0 (0%)	2 (15%)	2 (7%)
Cough	0 (0%)	3 (12%)	3 (6%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	2 (15%)	3 (11%)
Adverse events leading to treatment discontinuation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (7%)	2 (4%)	1 (7%)	0 (0%)	1 (4%)
Serious adverse events	0 (0%)	1 (4%)	1 (2%)	2 (11%)	3 (11%)	5 (11%)	2 (14%)	2 (15%)	4 (15%)
Infections	7 (32%)	9 (36%)	16 (34%)	4 (21%)	11 (41%)	15 (33%)	5 (36%)	8 (62%)	13 (48%)
Serious infections	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	1 (8%)	2 (7%)
Opportunistic infections	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (4%)
Malignancy	0 (0%)	1 (4%)[b]	1 (2%)	0 (0%)	1 (4%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Patients with one or more administration-site reactions	1 (5%)	0 (0%)	1 (2%)	1 (5%)	0 (0%)	1 (2%)	0 (0%)	1 (8%)	1 (4%)

[a]According to the Medical Dictionary for Regulatory Activities (MedDRA), descending total frequency.
[b]Occurred after week 28.

treatment resistant. In population 2, numerically greater clinical response was observed in patients who received intravenous administration compared with subcutaneous administration of ustekinumab; however, because of the small sample size and lack of placebo control, these observed results may represent random variation and should be interpreted with caution.

Ustekinumab generally was well tolerated. In population 1, the proportions of patients with one or more adverse events were slightly higher in the combined placebo group than in the combined ustekinumab group through week 8. Gastrointestinal adverse events were reported most commonly. Approximately twice as many patients who received placebo experienced worsening Crohn's disease than those who received ustekinumab. In both populations, the pattern of adverse events through week 28 was similar to that observed through week 8. Serious adverse events were uncommon and primarily related to Crohn's disease. Through week 28, infections were reported in similar proportions in the combined intravenous and combined subcutaneous ustekinumab groups. Two serious infections occurred: disseminated

histoplasmosis in a patient who recently had received infliximab and was receiving concurrent immunosuppressants, and viral gastroenteritis. Administration site reactions were uncommon among patients treated with ustekinumab. No patient tested positive for antibodies to ustekinumab.

Published literature regarding genetically deficient interleukin-12/23 mice or neutralizing interleukin-12/23 antibodies in mouse tumor models suggests that there may be an increased risk of malignancy with antagonism of interleukin-12/23 activity. Studies in mice have shown antagonism of interleukin-12/23 p40 subunit to be associated with both tumor-suppressing and -promoting effects.[33,34] However, more recent evidence suggests that Th17 cells are regulated differently in mice versus human beings.[35] The results of the present trial and 2 recently published large, randomized, double-blind, placebo-controlled ustekinumab trials[22,23] in patients with moderate-to-severe psoriasis do not suggest an increased risk of malignancy with ustekinumab therapy. Further studies are needed to better understand any association between antagonism of interleukin-12/23 activity and malignancy risk.

In conclusion, ustekinumab may induce clinical response in patients with moderate-to-severe active Crohn's disease. The effect was most prominent at 4–6 weeks and in patients treated previously with infliximab.

Ustekinumab Crohn's Disease Study Group

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