IM-UNITI

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IM-UNITI: 3 Year Efficacy, Safety, and Immunogenicity of Ustekinumab Treatment of Crohn's Disease

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Specific author contributions:

C Gasink, D Jacobstein, J Johanns, and OJ Adedokun participated in the conception and design of the study, participated in acquisition/collection of data, analysis and interpretation of data, and drafted/revised the manuscript for important intellectual content.

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B Zou participated in the analysis and interpretation of the data and drafted/revised the manuscript critically for important intellectual content.

All authors approved the final version of the manuscript for submission, including the authorship list.

Abbreviations: ADA, anti-drug antibody; AE, adverse event; CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; LTE, long-term extension; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; TNF, tumor necrosis factor

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ABSTRACT

Background and Aims: Following induction/maintenance treatment in the UNITI/IM-UNITI studies of ustekinumab for Crohn's disease, patients entered a long-term extension for up to 5 years from induction. Efficacy through 152 and safety through 156 weeks are reported.

Methods: At IM-UNITI Week 44, 567 ustekinumab-treated patients entered the long-term extension and continued to receive blinded subcutaneous ustekinumab on their assigned dose interval, without any subsequent dose adjustment. Placebo-treated patients discontinued after study unblinding (after IM-UNITI Week 44 analyses). Efficacy data in the LTE were collected every 12 weeks (q12w) prior to unblinding and then at q12w/q8w dosing visits.

Results: Through Week 156, 29.6% of ustekinumab-treated patients discontinued. In an intent-to-treat analysis of randomized patients from IM-UNITI Week 0-152, 38.0% of ustekinumab induction responders receiving drug q12w and 43.0% q8w were in remission at Week 152. Among patients entering the long-term extension in their original randomized groups, 61.9% of q12w and 69.5% of q8w patients were in remission at Week 152. Across all ustekinumab-treated patients (randomized and non-randomized) entering the long-term extension, remission rates at Week 152 were 56.3% and 55.1% for q12w and q8w, respectively.

Safety events (per hundred patient-years) were similar among all ustekinumab-treated patients entering the long-term extension and placebo (overall adverse events 389.70 vs 444.17; serious adverse events, 18.97 vs 19.54; serious infections, 4.21 vs 3.97). Rates of antibodies to

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ustekinumab through Week 156 remained low, 4.6% in all randomized ustekinumab-treated patients; lowest among patients in the original randomized q8w group (2/82, 2.4%).

Conclusion: Continued treatment with subcutaneous ustekinumab maintained clinical response and remission through 3 years in a majority of patients who responded to induction therapy and was well-tolerated. ClinicalTrials.gov number NCT01369355.

Keywords: ustekinumab, Crohn's disease, long-term

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease that usually requires long-term medical therapy to control symptoms and prevent disease-related complications.[1] Ustekinumab, a fully human monoclonal antibody to interleukin-12/23p40, is approved for the treatment of moderate-to-severe active CD. The efficacy and safety of ustekinumab in CD through 1 year has been previously established in the UNITI-1 and UNITI-2 (8 weeks) and IM-UNITI (44 weeks) studies.[2]

However, given the need for continued treatment in CD, the durability of response to biologic therapy is a critical clinical question of these agents for maintaining response and remission. Although multiple factors can result in discontinuation of therapy, including patient and or provider wishes, development of adverse events or biological resistance to a drug's mechanism of action, the development of antidrug antibodies (ADAs) to biologics is an important factor because they both could diminish drug efficacy and increase the risk of infusion or injection reactions.[3] Over the past two decades, multiple publications have documented the importance of sensitization in patients treated with tumor necrosis factor (TNF) antagonists, as well as other biologics.[4] The development of ADAs to infliximab is associated with an increased risk of infusion reactions and a reduced duration of response to treatment.[5] This problem also occurs with the fully humanized antibody, adalimumab. A review paper that included 23 adalimumab studies identified that the prevalence of ADAs was 0.3 to 38% and that their development was associated with reduced efficacy, loss of response, and high rate of secondary treatment failure.[6] In studies of certolizumab pegol ADAs were reported in 3.3-25% of patients.[6] In a recent analysis anti-vedolizumab antibodies were detected in 17% of patients during induction therapy

and 3% of patients during maintenance therapy, although no correlation was observed between clinical outcomes and the development of ADAs.[7] Additionally, it was noted that the low prevalence and transient nature of ADAs in patients who discontinued vedolizumab treatment may indicate that immunogenicity was not the key factor in treatment failure.[8]

The previous report of the IM-UNITI long-term extension (LTE) data through 2 years showed that subcutaneous ustekinumab maintained clinical response and remission through Week 92 and was well-tolerated.[9] The efficacy results for the IM-UNITI study through Week 152 and safety results through Week 156 presented here provide additional data on the long-term treatment effects of ustekinumab highlighting the sustainability of the clinical effects of ustekinumab through 3 years with continued low rates of immunogenicity.

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MATERIALS AND METHODS

Study Design and Endpoints

The ustekinumab program included 2 randomized, double blind, placebo-controlled 8-week induction studies (UNITI-1 and UNITI-2) as well as a maintenance phase through Week 44 (IM-UNITI). Detailed study design and efficacy results from the induction and maintenance study,[2] as well as results from the LTE through Week 96 have been previously published.[9]

Briefly, all patients who completed treatment through Week 44 of IM-UNITI were eligible to enter the LTE. Unblinding occurred after the Week 44 analyses (August 2015) and patients continued the same treatment they were receiving at Week 44 (subcutaneous [SC] placebo, ustekinumab 90 mg every 8 weeks [q8w] or every 12 weeks [q12w]); no dose adjustment occurred in the LTE. Placebo-treated patients were discontinued after unblinding. Efficacy assessments in the LTE were conducted q12w until unblinding and then q8w or q12w at dosing visits. As in the previous studies,[2, 9] clinical remission was defined as a Crohn's Disease Activity index (CDAI) score of <150 points and clinical response was defined as a reduction from Week 0 of UNITI- 1 or UNITI- 2 in the CDAI score of ≥100 points (or if a CDAI score of <150 was attained). Corticosteroid- free remission was defined as a CDAI score of <150 points without receiving corticosteroids at Week 152.

The populations included in the analyses were the same as those analyzed and detailed previously in the Week 96 manuscript[9] and are briefly described here. The randomized patient population included only those patients randomized in the maintenance trial who continued into the LTE (ustekinumab 90 mg q12w- patients randomized to q12w dosing in maintenance with no

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dose adjustment; ustekinumab 90 mg q8w-patients randomized to q8w dosing in maintenance with no dose adjustment; dose adjusters-all patients who dose adjusted between Weeks 8 and 32 during maintenance [Placebo→ ustekinumab q8w, ustekinumab q12w→q8w, ustekinumab q8w→q8w]). Dose adjustment was not permitted in the LTE. The all patient population included all patients who entered the LTE (randomized and non-randomized patients) who received ustekinumab q8w or every q12w (Figure 1).

The incidence of antibodies to ustekinumab was evaluated, using a validated, drug-tolerant electrochemiluminescence immunoassay (ADA detected in up to 100 µg/mL of ustekinumab without interference), for all treated patients who entered the LTE and received at least 1 administration of ustekinumab, either in the induction studies (UNITI-1 or UNITI-2) or IM-UNITI (through Week 44), and had appropriate samples for detection of antibodies to ustekinumab (i.e., patients with at least 1 sample obtained after their first dose of ustekinumab). The relationships between antibody to ustekinumab status through Week 152 and clinical response and remission status, as well as injection-site reactions through Week 152 were explored.

Statistical Analysis

Because placebo patients discontinued the study after treatment assignments were unblinded to investigative sites (after the last patient completed Week 44 and database lock and subsequent analyses were completed), direct comparisons and/or statistical comparisons of efficacy results between placebo and ustekinumab treatment groups throughout the extension were not considered appropriate for efficacy endpoints. Instead, summaries of the data for the ustekinumab groups are provided.

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Demographic and baseline disease characteristics, efficacy, and safety analyses were based on all patients treated with at least 1 administration of study agent during the LTE. Descriptive statistics (eg, mean, median, standard deviation, interquartile range, minimum, and maximum) were used to summarize continuous variables. Counts and percentages were used to summarize categorical variables. Kaplan-Meier curves were provided for the time to loss of response analysis.

The analyses conducted evaluated (1) All randomized patients in maintenance, regardless of whether they entered the LTE (intent-to-treat analysis of randomized patients from Week 0 of IM-UNITI), (2) Patients who entered LTE (randomized patients and all patients), (3) observed cases with inclusion only of randomized patients who entered the LTE and who had data at a designated visit.

For all efficacy analyses, patients with a CD-related surgery or who discontinued study agent due to lack of efficacy or an adverse event indicated to be worsening CD after Week 44 and prior to the designated analysis time point were considered not to be in clinical remission/response, regardless of their CDAI score. Patients with insufficient data to calculate the CDAI score at the designated analysis time point were considered not to be in clinical remission/response (patients were excluded for the observed case analysis). Other dichotomous endpoints followed the same treatment failure and missing data rules.

For continuous endpoints, patients meeting these treatment failure rules prior to the designated analysis time point had their induction baseline value carried forward and if there was insufficient data to calculate the variable at the designated analysis time points their last value was carried forward.

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RESULTS

Baseline Characteristics

Upon completion of Week 44 of IM-UNITI, 567 ustekinumab patients entered into the LTE. Of these, 237 patients were from the primary population (induction responders to ustekinumab re-randomized at Week 0 of maintenance) including 84 patients receiving q12w ustekinumab and 153 patients receiving q8w ustekinumab, 71 of whom had undergone dose adjustment (Figure 1; Supplemental Figure 1). Clinical characteristics for the population of patients enrolled in the 3-year LTE were the same for those reported in the 2-year LTE.[9] Among randomized patients, median CDAI score at Week 44 was similar in patients in the ustekinumab q8w (70.5) and q12w (95.5) groups and higher in dose adjustment group (130.0; Table 1). The proportion of randomized patients in clinical remission at Week 44 was lower in the dose adjustment group (63.4%) than in the ustekinumab q8w (84.1%) and q12w (77.4%) groups. Clinical characteristics were similar for the all patient population (Table 1).

Discontinuation

Rates of discontinuation of study agent through Week 156 from the original randomized patients were 22.0%, 27.4%, and 33.8% in the ustekinumab q8w, q12w, and dose adjuster groups, respectively (Table 2). Among all randomized patients who received ustekinumab, the most common reasons for discontinuation of study agent were adverse events (AEs), lack of efficacy, physician decision, lost to follow-up, and withdraw of consent. In the placebo group 93.4% of patients discontinued study agent; 65.6% due to per-protocol study unblinding.

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Efficacy

Intent-to-treat analysis of randomized patients from Week 0 of maintenance

The proportions of patients in clinical remission from Week 44 to Week 152 in both the ustekinumab treatment groups were 53.1% to 43.0% and 48.8% to 38.0% in the q8w and q12w groups, respectively (Figure 2A). Similar trends were observed among randomized TNF-naïve patients from Week 44 through Week 152 (Figure 2B).

Randomized patients entering long-term extension

Through year 3 of the IM-UNITI LTE, both the ustekinumab q8w and q12w doses performed similarly for most clinical measures with a slightly higher percentage of patients in clinical remission at Week 152 among patients receiving ustekinumab q8w (69.5%) than patients receiving ustekinumab q12w (61.9%) (Table 3). From Week 92 through Week 152, a substantial percentage of patients maintained remission in both the UNITI-1 population (70.4% to 59.3%, respectively for the ustekinumab q8w group and 59.4% to 43.8%, respectively for the ustekinumab q12w group) and UNITI-2 population (80.8% to 73.1%, respectively in the ustekinumab q8w group and 76.4% to 74.5%, respectively, in the q12w group). Maintenance of remission was more stable among the UNITI-2 populations (Figure 3).

Percentages of patients with steroid-free remission (remission and not receiving corticosteroids) at Week 152 were higher in both the ustekinumab 90mg q8w and q12w groups (61.0% and 54.8%, respectively) compared with those receiving dose adjustment (39.4%; Table 3). In both ustekinumab groups, among patients who were receiving corticosteroids at maintenance baseline, 73.5% were able to eliminate corticosteroid use by Week 152, compared with 52.6% of patients

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who had dose adjusted (Supplemental Figure 2). A post-hoc analysis, showed that sustained corticosteroid-free remission (at weeks 128, 140, and 152) was achieved by 53.7% (44/82) and 47.6% (40/84) patients in the ustekinumab 90mg q8w and q12w groups, respectively, compared with 32.4% (23/71) of those who dose adjusted.

Patients in the ustekinumab q8w and q12w groups achieved median reductions from CDAI maintenance baseline scores of 38.5 and 39.5 points, respectively, compared with a 15.0-point decrease in those patients who had a prior dose adjustment (Table 3). Median (C-reactive protein) CRP over time was stable and similar in both ustekinumab q8w and q12w groups (Supplemental Figure 3).

The difference in the time to loss of response from Weeks 44 to 152 between the ustekinumab q8w group and q12w group was statistically significant (log rank test p=0.044, Figure 4). The time to loss of response was longer for the q8w group compared with the q12w group.

All treated patients entering long-term extension

At Week 152, 55.1% and 56.3% of patients in the ustekinumab q8w and q12w groups were in remission (Figure 5). From Week 92 to Week 152, rates of remission were generally maintained in both ustekinumab groups (64.4% to 55.1% in the q8w group and 64.3% to 56.3% in the q12w group, respectively).

No association was observed between immunomodulator and corticosteroid use at Week 44 and long-term remission at Week 152. Patients without prior stricturing disease had higher rates of remission at Week 152 in the ustekinumab q8w and q12w groups.

Observed case analysis of randomized patients entering long-term extension

Higher proportions of patients achieved remission at Week 152 in the ustekinumab q8w group than in the ustekinumab q12w group (82.6% and 74.3%, respectively; Supplemental Figure 4).

Safety

All treated patients entering long-term extension

Week 0-Week 156

From Week 0 through Week 156, safety events (per hundred patient-years) were similar among all ustekinumab-treated patients compared to placebo, including overall adverse events (389.70 vs 444.17), serious adverse events (18.97 vs 19.54), and serious infections (4.21 vs 3.97), respectively, with an average of 141.7 weeks and 1544.8 patients-years of follow-up for all ustekinumab-treated patients (Table 4).

Week 44-Week 156

From Week 44 through Week 156, safety events (per hundred patient-years) were similar among all ustekinumab-treated patients compared to placebo, including overall adverse events (325.26 vs 358.80), serious adverse events (19.40 vs 23.11), and serious infections (4.14 vs 4.62), respectively, with an average of 97.4 weeks and 1061.6 patients-years of follow-up for all ustekinumab-treated patients (data not shown).

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Among all patients entering the LTE, 48 patients had one or more serious infections. Serious infections occurring in 2 or more ustekinumab-treated patients included: anal abscess (1.4%), pneumonia (0.7%), cellulitis (0.4%), gastroenteritis (0.4%), perirectal abscess (0.4%), pyelonephritis (0.4%), and sepsis (0.4%). Other serious infections of interest included cytomegalovirus colitis and liver abscess in two patients receiving placebo.

Overall, 4 solid and hematologic malignancies were reported which included testicular seminoma, adenocarcinoma of small intestine, chronic myeloid leukemia in patients on ustekinumab in the study extension and a papillary thyroid cancer in a patient who remained on placebo throughout the study. Through 3 years, seven non-melanoma skin cancers were reported, of which 5 patients had prior or concomitant exposure to thiopurines. There were 4 basal cell carcinomas: 2 reported from Week 96 through Week 156 in patients who received ustekinumab induction and maintenance and as previously reported, 1 patient who received ustekinumab induction and maintenance and 1 patient who received placebo induction/ ustekinumab maintenance /ustekinumab LTE; and 3 squamous cell carcinomas: 1 reported from Week 96 through Week 156 in a single patient on placebo induction/ ustekinumab maintenance /ustekinumab LTE; and as previously reported, 1 patient on ustekinumab induction/placebo maintenance/LTE and 1 patient on placebo only.

One case of tuberculosis was previously reported (deemed unrelated to study drug and completely resolved with therapy) in the long-term extension.[9] No new cases on TB occurred in the third year.

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Six deaths were reported from Week 44 through Week 156. Three were reported from Week 96 through Week 156; including individual patients with end stage renal disease, acute myocardial infarction and septic shock. None of the deaths were deemed related to ustekinumab.

Immunogenicity in the randomized population

The rates of antibodies to ustekinumab formation (using a sensitive drug-tolerant assay) remained low through Week 156 with 4.6% (11/237) of all ustekinumab treated patients testing positive for antibodies to ustekinumab at any point during maintenance through Week 156. Rates were higher in patients who were initially assigned to placebo, 8.2% (Table 5). Rates were lowest among patients who remained on continuous q8w dosing without dose adjustment (2/82, 2.4%; Table 5). Rates of antibody formation were similar between patients not receiving concomitant immunosuppressive at Week 44 (7/157, 4.5%) compared to those on immunosuppressives at Week 44 (4/80, 5.0%; Supplemental Table 1). There was no apparent relationship across the various randomized groups between antibody status and efficacy (Supplemental Table 2).

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DISCUSSION

IM-UNITI is a 5-year maintenance study designed to evaluate the efficacy and safety of long-term ustekinumab therapy for CD. Previously published data demonstrated that in ustekinumab induction responders, remission and response rates were maintained through the original primary endpoint at Week 44[2] and subsequently through Week 92.[9] Here, we report that in ustekinumab induction responders, remission and response rates were generally maintained in both TNF antagonist failure and non-failure populations through Week 152. Consistent with the previously reported data, rates of maintenance of remission were more stable among the TNF antagonist non-failure population and in patients who had not experienced dose adjustment prior to Week 44. Non-randomized patients performed similarly to the randomized population. Both q8w and q12w week ustekinumab SC dosing regimens were effective and the difference between the dosing regimens was not clinically meaningful from Week 92 to Week 152.

The efficacy analyses presented here, all demonstrating substantial maintenance of efficacy through 3 years, are comprehensive. They include analysis of patients who entered the LTE (both randomized and all patients), observed case analysis with inclusion only of randomized patients who entered the LTE who have data at that visit, and analysis of all randomized patients in maintenance, regardless of whether they entered the LTE. The latter was performed according to the intent-to-treat principle and therefore provides conservative efficacy estimates for the randomized population from the beginning of maintenance. Additionally, all patients remained on stable dosing without dose adjustment in the LTE. It is notable that 43% of the q8w and 38% of the q12w SC ustekinumab groups are in remission at Week 152 using this most stringent analysis. The observed case analysis is presented since it is often included in other biologic LTE

publications [10-12] and demonstrates the range of results depending on the analysis, with 83% of the q8w and 74% of the q12w ustekinumab groups in remission at Week 152.

The low immunogenicity rates of ustekinumab may be related to the maintenance of response in CD. Formation of ADAs is thought to be one of the most important causes of loss of response to anti-TNF agents and development of ADAs to infliximab can lead to an increased risk of infusion reaction and reduced duration of response.[5] In addition, antibody formation may accelerate drug clearance due to the formation of immune complexes.[13] The potential for immunogenicity of biologics can be influenced by multiple factors that may be molecule, patient, or assay related. The use of the drug-tolerant assay used in this study may remove some of the questions around assay-related immunogenicity. Although the precise reason for the low immunogenicity profile of ustekinumab is unknown, it may be that the molecule itself and the mechanism of action are responsible for the low immunogenic profile.

Cross compound comparison of immunogenicity is challenging, due to differences in immunogenicity assays and study design. However, a recent systematic review reported the highest rates in infliximab and adalimumab, followed by certolizumab pegol, with lower rates observed in ustekinumab and golimumab treated patients.[14] While rates of ADA formation were low in the pivotal CD and UC studies of vedolizumab, 3.7-4.1%,[15, 16] a recent study reported anti-vedolizumab antibodies were detected in 17% of patients during induction therapy and 3% of patients during maintenance therapy, although no correlation was seen with clinical outcomes[7] and immunogenicity was not considered a key factor in treatment failure.[8] Rates of antibodies to ustekinumab in the randomized CD Phase 3 program were low; 2.3% through Week 44,[2] 4.2% at

Week 96,[9] and 4.6% through Week 156, and were low either with or without the use of concomitant immunomodulators. Antibody positivity was not related to efficacy.

Despite the longer follow-up, the safety data in this manuscript are consistent with the safety previously reported in ustekinumab CD studies[2, 9] and with ustekinumab long-term treatment of psoriasis.[17-19] The overall rates of adverse events and serious adverse events were comparable to placebo through Week 156. No new safety signals were identified between Weeks 96 and 156. Rates of serious infection and malignancy remained low and use of concomitant therapies did not appear to influence the overall safety or efficacy of ustekinumab. While the 3-year data is reassuring, limited numbers of patients may not allow detection of rare events.

Limitations to the LTE have been previously discussed.[9] Additionally, it should be noted that since there was no opportunity for patients to dose-escalate in this LTE, proportions of patients remaining on ustekinumab maintenance in this study may be lower than what would be seen in real-world practice, where such escalation is possible.

In conclusion, SC ustekinumab maintained clinical response and remission through 3 years in a substantial proportion of patients, including a unique intent-to-treat population, and in particularly those who were naïve to TNF antagonists. Immunogenicity rates remained low, were not lower in patients on concomitant immunosuppressives, and antibodies did not seem to affect clinical outcomes. Ustekinumab was well-tolerated through 3 years, with no new safety signals observed.

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FIGURE LEGENDS

Figure 1. Study design and patient flow for IM-UNITI LTE

Figure 2. Patients in clinical remission over time through Week 152 among (**A**) all randomized patients from baseline of IM-UNITI and (**B**) randomized TNF-naïve patients from baseline of IM-UNITI

Figure 3. Patients in clinical remission over time by induction (UNITI-1 or UNITI-2) study among randomized patients who entered the long-term extension

Figure 4. Kaplan-Meier curve for the time to loss of response from Week 44 through Week 152 for randomized patients who were responders to ustekinumab at Week 44, had never been dose adjusted, and entered into the long-term extension

Figure 5. Patients in clinical remission over time through Week 152 among all patients who entered the long-term extension

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TABLES

Table 1. Summary of CDAI, CRP, IBDQ values and clinical remission status at Week 44 of maintenance among randomized patients (A) and all patients (B) who entered the LTE

Randomized patients

	Placebo	Ustekinumab 90 mg q12w	Ustekinumab 90mg q8w	Dose adjusters[a]
N	61	84	82	71
Median CDAI	96.0	95.5	70.5	130.0
Median IBDQ	180.5	189.0	185.5	171.0
Median CRP	6.7	3.5	3.7	4.0
Patients in clinical remission	77.0%	77.4%	84.1%	63.4%

All patients who entered the LTE

	Placebo	Ustekinumab 90 mg q12w	Ustekinumab 90mg q8w[b]	Combined ustekinumab
N	151	213	354	567
Median CDAI	97.0	109.0	111.0	110.0
Median IBDQ	179.0	179.0	174.0	175.0
Median CRP	6.0	4.4	3.7	3.8
Patients in clinical remission	72.2%	68.5%	68.9%	68.8%

[a] Dose-adjusters were receiving subcutaneous ustekinumab 90 mg q8w [b-] Dose-adjusters are included in the ustekinumab 90mg q8w group

CDAI, Crohn's Disease Activity Index; CRP, c-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; LTE, long-term extension; q12w, every 12 weeks; q8w, every 8 weeks

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Table 2. Number of patients who discontinued study agent through week 156[a]

	Placebo	Ustekinumab 90mg q12w	Ustekinumab 90mg q8w	Dose adjusters[b]
N	61	84	82	71
Patients who discontinued N (%)	57 (93.4%)	23 (27.4%)	18 (22.0%)	24 (33.8%)
Reason for discontinuation				
Adverse events	11.5%	6.0%	8.5%	12.7%
Lack of efficacy	8.2%	6.0%	2.4%	8.5%
Protocol violation	0	0	0	0
Study terminated by sponsor	0	0	0	0
Physician decision	0	1.2%	2.4%	1.4%
Lost to follow-up	1.6%	1.2%	1.2%	0
Withdraw of consent	6.6%	11.9%	7.3%	8.5%
Death	0	1.2%	0	2.8%
Placebo patients discontinued due to unblinding	65.6%	0	0	0

[a]Randomized patients who entered the LTE
[b]Dose-adjusters were receiving subcutaneous ustekinumab 90 mg q8w q12w; every 12 weeks; q8w, every 8 weeks

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Table 3. IM-UNITI Efficacy Assessments at Week 152 Among Randomized Patients who entered LTE[a]

	Ustekinumab				
		90mg SC q8w			All ustekinumab
	90 mg SC q12w	90mgSC q8w	Prior dose adjustment	Combined	
N	84	82	71	153	237
Clinical remission N (%)	52 (61.9%)	57 (69.5%)	34 (47.9%)	91 (59.5%)	143 (60.3%)
Clinical response N (%)	57 (67.9%)	63 (76.8%)	43 (60.6%)	106 (69.3%)	163 (68.8%)
Clinical remission at Week 152 and not receiving corticosteroids at week 152 N (%)	46 (54.8%)	50 (61.0%)	28 (39.4%)	78 (51.0%)	124 (52.3%)
Clinical remission in UNITI-1 subset N	32	27	32	59	
N (%)	14 (43.8%)	16 (59.3%)	14 (43.8%)	30 (50.8%)	
Clinical remission in the UNITI-2 subset N	52	55	39	94	
N (%)	38 (73.1%)	41 (74.5%)	20 (51.3%)	61 (64.9%)	
Median change from maintenance baseline CDAI	-39.5	-38.5	-15.0	-30.0	-35.0

[a]Patients who had insufficient data at the designated analysis time point are considered not to be in clinical remission or response
CDAI: Crohn's disease activity index; LTE: long-term extension; Pts: patients; q12w: every 12 weeks; q8w: every 8 weeks; SC: subcutaneous.

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Table 4. Summary of key safety findings per 100 patient-years of follow-up from Week 0 through Week 156; all patients entering LTE

	Placebo	Ustekinumab 90mg q12w	Ustekinumab 90mg q8w	Combined ustekinumab
N	151	213	354	567
Average duration of follow-up (weeks)	104.0	142.9	140.9	141.7
Total patient-years of follow-up	301.9	585.4	959.4	1544.8
Deaths	0	2	4	6
Number of specified events per hundred patient-years of follow-up (95% CI)				
Adverse events	444.17 (420.71, 468.59)	362.00 (346.75, 377.75)	406.60 (393.94, 419.56)	389.70 (379.92, 399.67)
Serious adverse events	19.54 (14.88, 25.21)	19.30 (15.91, 23.21)	18.76 (16.12, 21.71)	18.97 (16.86, 21.27)
Infections	100.36 (89.38, 112.32)	106.43 (98.24, 115.13)	108.29 (101.81, 115.08)	107.59 (102.48, 112.89)
Serious infections	3.97 (2.05, 6.94)	5.98 (4.16, 8.32)	3.13 (2.11, 4.46)	4.21 (3.25, 5.36)

CI, confidence interval; LTE, long-term extension; q8w, every 8 weeks; q12w, every 12 weeks;

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Table 5. Summary of antibody to ustekinumab status in randomized patients during IM-UNITI through Week 156

		ustekinumab				
			90 mg SC q8w			
	placebo SC[a]	90 mg SC q12w[a]	90 mg SC q8w	prior dose adjustment[b]	combined	all ustekinumab
N[c]	61	84	82	71	153	237
Antibody status N (%)						
Positive for antibodies to ustekinumab at any time through Week 156[d,e]	5 (8.2%)	4 (4.8%)	2 (2.4%)	5 (7.0%)	7 (4.6%)	11 (4.6%)
Negative for antibodies to ustekinumab through Week 156[d,f]	56 (91.8%)	80 (95.2%)	80 (97.6%)	66 (93.0%)	146 (95.4%)	226 (95.4%)

[a] Patients who were in clinical response to ustekinumab intravenous induction dosing, were randomized to receive study drugs on entry into the maintenance study, and did not meet loss of response criteria from Week 8 through Week 32.
[b] Patients who were in clinical response to ustekinumab induction dosing, were randomized, met loss of clinical response criteria from Week 8 through Week 32, and initiated ustekinumab 90 mg SC q8w (for patients randomized to receive placebo SC or ustekinumab 90 mg SC q12w on entry into the maintenance study) or continue ustekinumab 90 mg SC q8w (for patients randomized to receive ustekinumab 90 mg SC q8w on entry into the maintenance study) in this maintenance study.
[c] Patients with appropriate samples had 1 or more samples obtained after their first study agent administration of maintenance study.
[d] Denominator is patients with appropriate samples.
[e] Includes all patients who had at least 1 positive sample at any time in this maintenance study.
[f] Excludes patients who were positive at any time through Week 156 in this maintenance study and includes patients whose samples may contain ustekinumab.
q12w, every 12 weeks; q8w, every 8 weeks; SC, subcutaneous

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Table 6. Summary of antibody to ustekinumab status through Week 156 by dose adjustment status prior to Week 44; Patients who were randomized and entered into LTE

	Ustekinumab							
				90 mg SC q8w				
		On 90 mg SC q8w due to dose adjustment prior to week 44						
	Placebo SC[a]	90 mg SC q12w	90 mg SC q8w	90 mg SC q8w→90 mg SC q8w	placebo SC → 90 mg SC q8w	90 mg SC q12w → 90 mg SC q8w	All 90 mg SC q8w	All ustekinumab
N[b]	61	84	82	17	35	19	153	237
Antibody status								
Positive for antibodies to ustekinumab at any time through Week 156[c]	5 (8.2%)	4 (4.8%)	2 (2.4%)	1 (5.9%)	3 (8.6%)	1 (5.3%)	7 (4.6%)	11 (4.6%)
Negative for antibodies to ustekinumab through Week 156[c,e]	56 (91.8%)	80 (95.2%)	80 (97.6%)	16 (94.1%)	32 (91.4%)	18 (94.7%)	146 (95.4%)	226 (95.4%)

a Patients who were in clinical response to ustekinumab IV induction dosing, were randomized to receive study drugs on entry into the maintenance study, and did not meet loss of response criteria from Week 8 through Week 32.
b Patients with appropriate samples had 1 or more samples obtained after their first study agent administration of this maintenance study.
c Denominator is patients with appropriate samples.
d Includes all patients who had at least 1 positive sample at any time in this maintenance study.
e Excludes patients who were positive at any time through Week 156 in this maintenance study and includes patients whose samples may contain ustekinumab.
LTE, long-term extension; SC, subcutaneous; q12w, every 12 weeks, q8w, every 8 weeks

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FIGURES

Figure 1.

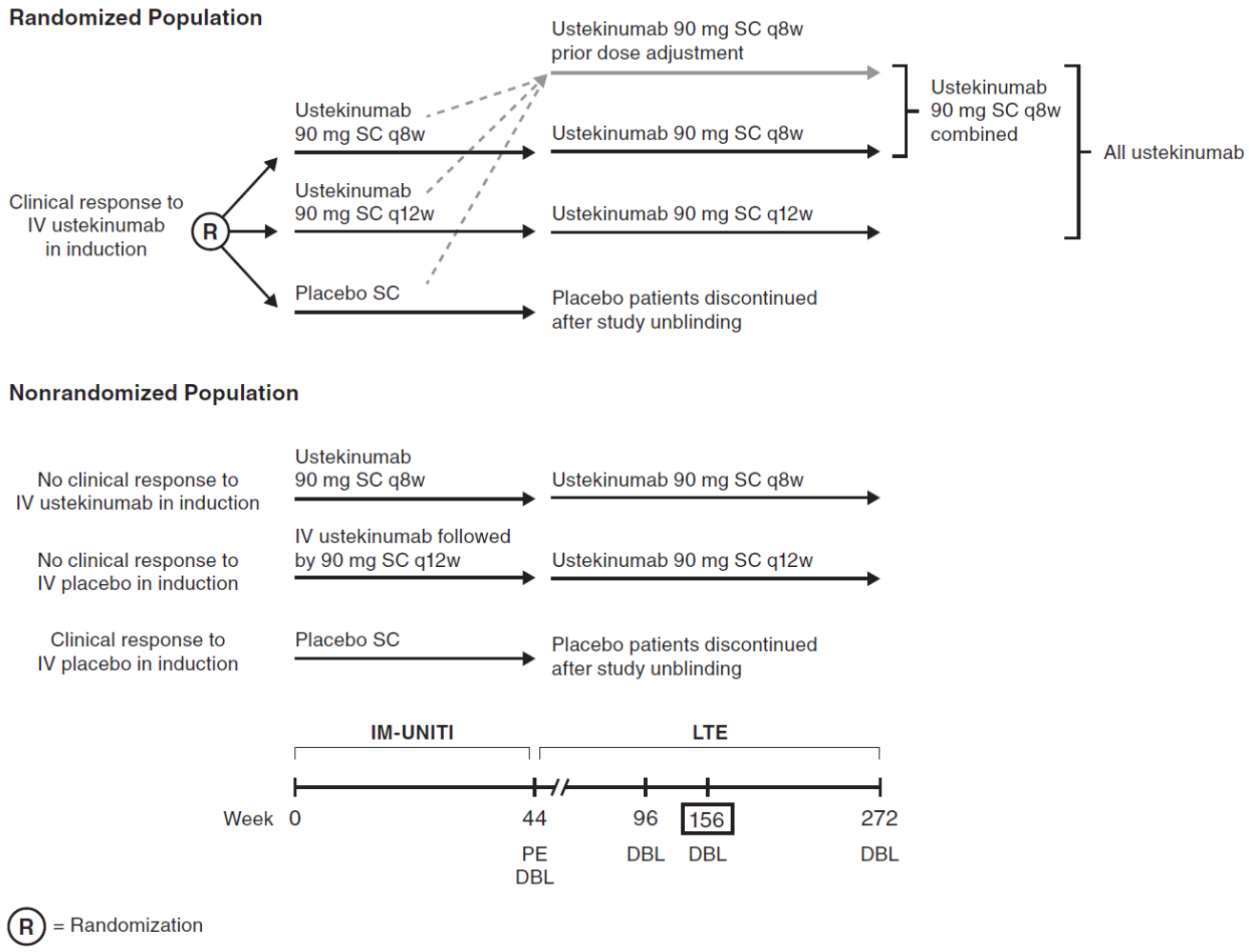

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Figure 2

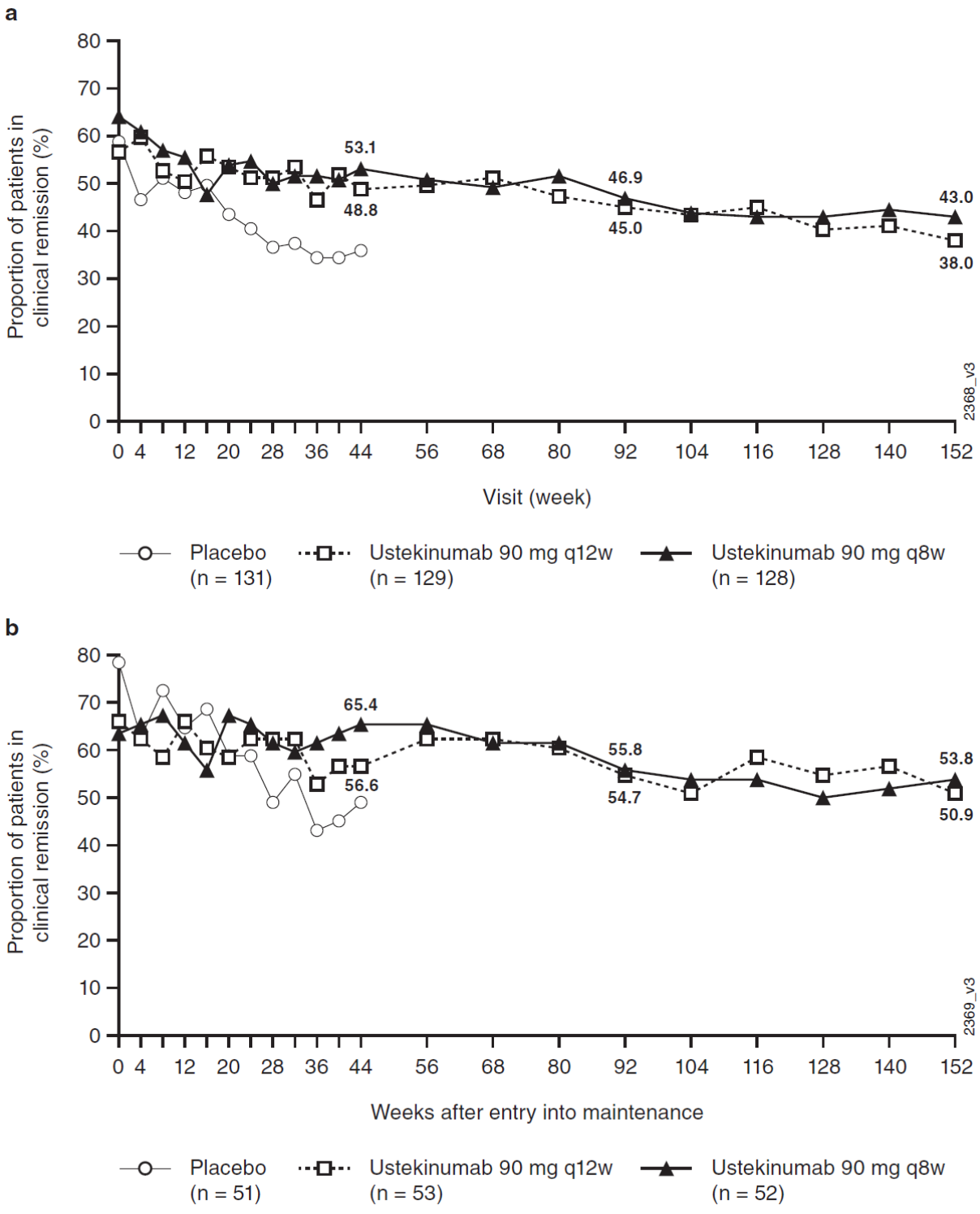

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Figure 3.

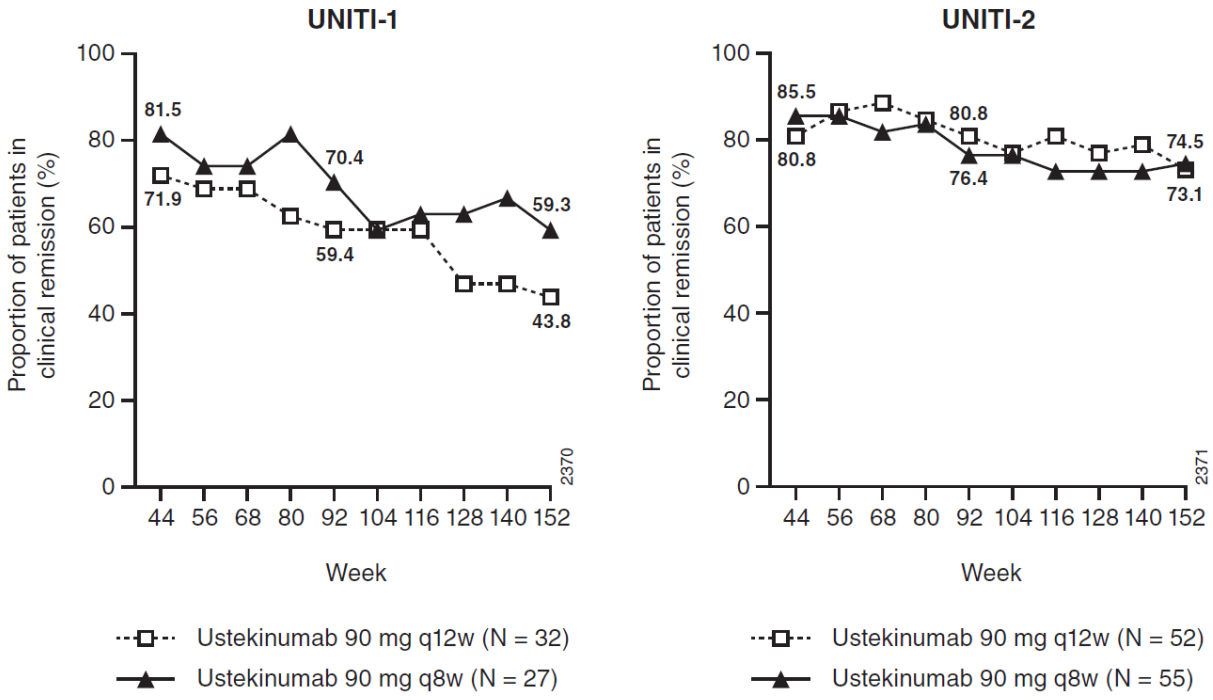

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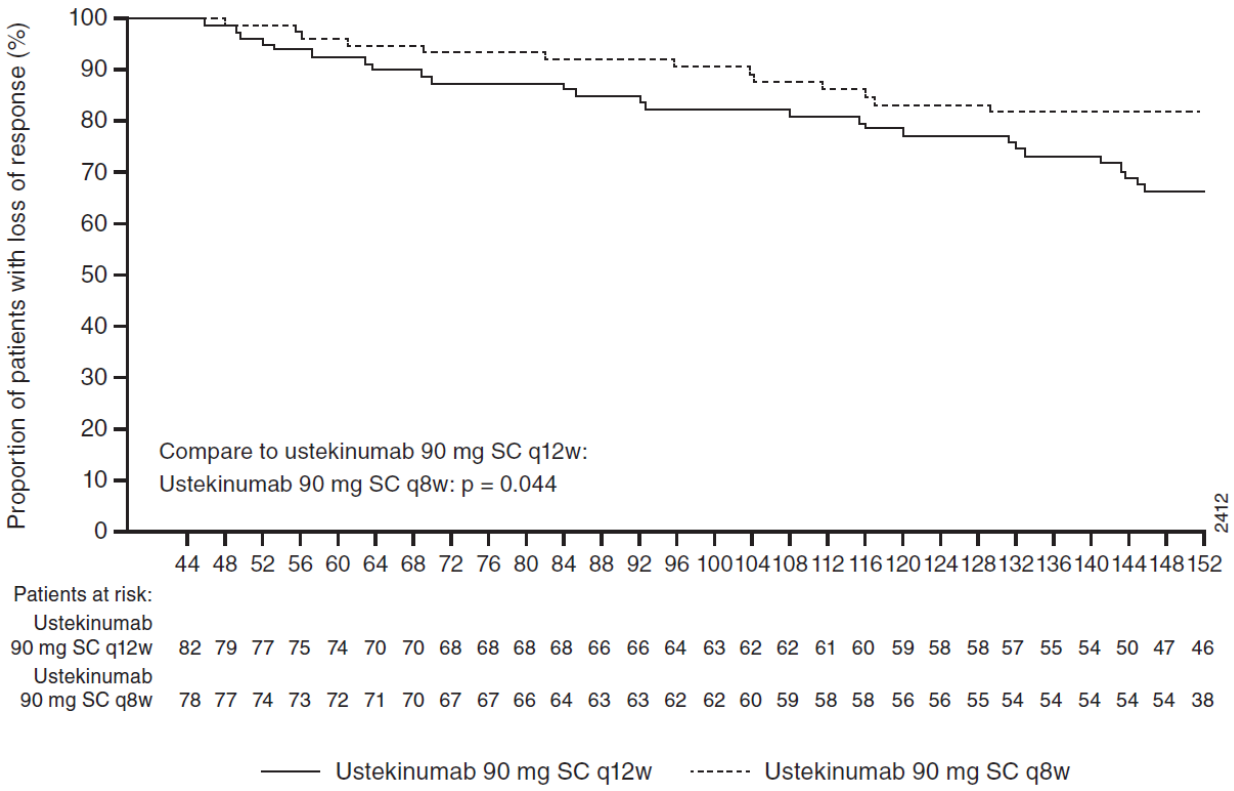
Figure 4.



CDAI, Crohn's disease Activity Index; q12w, every 12 weeks; q8w, every 8 weeks; SC ,subcutaneous

Note:

Ustekinumab 90 mg SC q12w: Patients who were in clinical response to ustekinumab IV induction dosing, were randomized to receive ustekinumab 90 mg SC q12w on entry into the maintenance study, and did not meet loss of response criteria from Week 8 through Week 32, and were responders at Week 44.

Ustekinumab 90 mg SC q8w: Patients who were in clinical response to ustekinumab IV induction dosing, were randomized to receive ustekinumab 90 mg SC q8w on entry into the maintenance study, and did not meet loss of response criteria from Week 8 through Week 32, and were responders at Week 44.

Time to loss of response (Weeks) are calculated from Week 44 to the date of first loss of response (based on observed CDAI assessment date), or the first treatment failure date, whichever earlier. Patients who did not lose response prior to or at Week 152 are censored at the last CDAI assessment date.

Treatment failure is defined as: Patients received a prohibited Crohn's disease-related surgery, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn's disease after week 44.

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Figure 5.