EFFICACY AND SAFETY OF USTEKINUMAB FOR ULCERATIVE COLITIS THROUGH 4 YEARS: FINAL RESULTS FROM THE UNIFI LONG-TERM EXTENSION

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B.E. Sands,[1] M.T. Abreu,[2] S. Danese,[3] W.J. Sandborn,[4] Y. Miao,[5] H. Zhang,[5] R. Panaccione,[6] T. Hisamatsu,[7] E.J. Scherl,[8] R.W. Leong,[9] D.S. Rowbotham,[10] R.P. Arasaradnam,[11] L. Peyrin-Biroulet,[12] W. Afif,[13] C. Marano[5]

[1]Dr. Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]University of Miami Miller School of Medicine, Miami, FL, USA; [3]Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milano, Italy; [4]Division of Gastroenterology, University of California San Diego, La Jolla, CA, USA; [5]Janssen Research & Development, LLC, Spring House, PA, USA; [6]University of Calgary, Calgary, AB, Canada; [7]Department of Gastroenterology and Hepatology, Kyorin University School of Medicine, Tokyo, Japan; [8]Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY, USA; [9]Concord Hospital and Macquarie University Hospital, Sydney, New South Wales, Australia; [10]Auckland City Hospital, Auckland, New Zealand; [11]Warwick Medical School, University of Warwick & University Hospital Coventry, Coventry Warwickshire, UK; [12]Gastroenterology Department and Inserm U954, Nancy University Hospital, Vandœuvre-lès-Nancy, France; [13]Division of Gastroenterology, McGill University Health Centre, Montréal, Québec, Canada

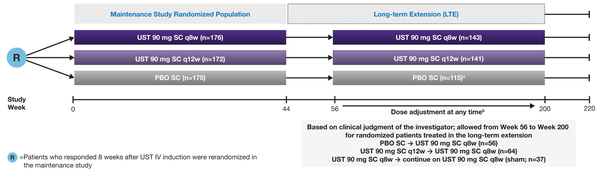
BACKGROUND/OBJECTIVE

- Ustekinumab (UST) is an interleukin-12/23 p40 antagonist approved for the treatment of moderate-to-severe ulcerative colitis (UC)
- The UNIFI long-term extension (LTE) evaluated subcutaneous (SC) 90 mg UST maintenance therapy through 4 years
- **Here, we report the final efficacy and safety data through 4 years of UST treatment, including subpopulations based on biologic treatment history**

METHODS

- 523 intravenous (IV) UST induction responders were randomized to SC maintenance therapy[1,2]
  - 176 UST 90 mg every 8 weeks (q8w); 172 UST 90 mg q12w; 175 SC placebo (PBO) (**Figure 1**)
- The nonrandomized population included:
  - UST induction nonresponders at Week 8 who received SC UST, responded 8 weeks later, and continued to receive UST q8w
  - Responders to PBO induction who received SC PBO
- Patients who completed Week 44 were eligible to continue treatment in the LTE
- PBO patients were discontinued after study unblinding
- Starting at Week 56, randomized patients with UC worsening could adjust to q8w
- Efficacy was evaluated in UST-randomized patients (n=348) using symptomatic remission
  - Mayo stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0
- Inflammatory biomarkers C-reactive protein (CRP) and fecal calprotectin were measured
- Disease-specific health-related quality of life was evaluated using the Inflammatory Bowel Disease Questionnaire (IBDQ)
- Safety was evaluated for all 588 patients treated in the LTE, including randomized and nonrandomized populations

Figure 1. UNIFI Study Design



[a]Patients who remained on PBO were discontinued from the LTE after maintenance study unblinding, which occurred after analysis of the maintenance Week 44 study data
[b]Those patients randomized to PBO and those randomized to UST q8w were only eligible for dose adjustment prior to unblinding

CONCLUSIONS

- **Patients with moderate-to-severe UC receiving SC UST generally maintained clinical benefit through 4 years**
- **No new safety signals were observed through the final year of the UNIFI study**

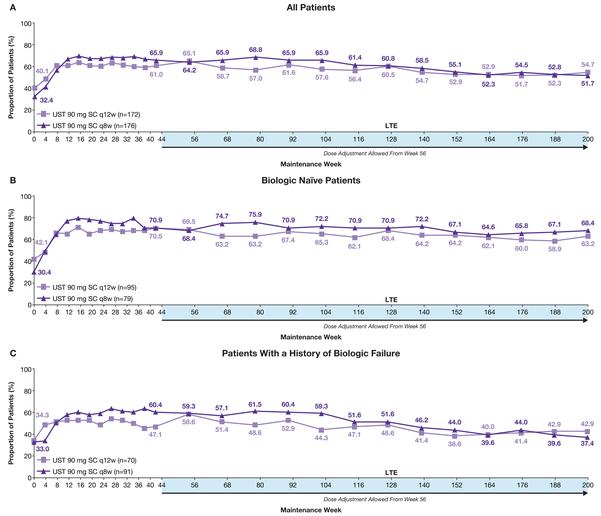
RESULTS

Patients Randomized to UST at Maintenance Baseline (Intent-to-treat (ITT) population)

Symptomatic Remission at Week 200

- The proportion of patients in symptomatic remission at Week 200 were:
  - 55.2% of all patients (q8w and q12w combined)
    - 67.2% of biologic naïve patients
    - 41.6% of patients with a history of biologic failure
- 53.2% of all patients (q8w and q12w combined) achieved corticosteroid-free symptomatic remission at Week 200 (**Figure 2A-C**)

Figure 2. Corticosteroid-free Symptomatic Remission Through Week 200 in Patients Randomized to Receive UST at Week 0 of Maintenance[a-f]



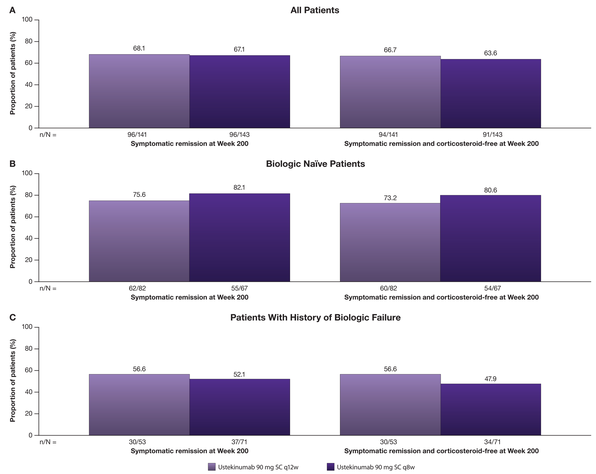
[a]Patients were included in the randomized group at maintenance Week 0 regardless of whether patients had a dose adjustment during the LTE. [b]Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0. [c]Patients who had a missing value in corticosteroid use had their last value carried forward. [d]Patients who had both stool frequency and rectal bleeding subscores missing at a visit were considered not to be in symptomatic remission for that visit. [e]Patients who had a prohibited change in UC medication, an ostomy or colectomy, or used a rescue medication after clinical flare, or discontinued study agent due to lack of therapeutic effect or due to an adverse event of worsening of UC prior to the designated visit before or at Week 44 were considered not to be in symptomatic remission. [f]Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an adverse event of worsening of UC after Week 44 and prior to the designated visit were considered not to be in symptomatic remission

Randomized Patients Who Continued UST Treatment in the LTE

- 67.6% were in symptomatic remission at Week 200[1]
- 72.9% of those in clinical remission at Week 44 were in symptomatic remission at Week 200[1]
- 94 of 96 (98%) patients achieving symptomatic remission in the UST 90 mg SC q12w treatment group were corticosteroid-free at Week 200, as were 91 of 96 (95%) patients in the UST 90 mg SC q8w treatment group[1] (**Figure 3**)
- 42.7% of patients with history of biologic failure and 18.8% of biologic naïve patients discontinued treatment between Weeks 44 and 200
- 85.1% of patients with observed data who had not met treatment failure criteria were in symptomatic remission at Week 200

[1]*With nonresponder imputation for missing data and treatment failure criteria*

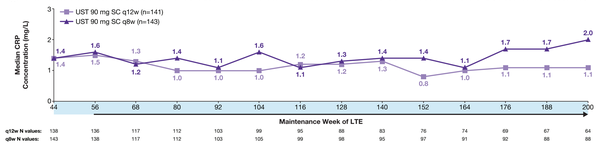
Figure 3. Symptomatic Remission and Corticosteroid-free Symptomatic Remission at Week 200 for Patients Randomized in Maintenance and Continued UST Treatment in the LTE[a-e]



[a]Patients were included in the randomized group at maintenance Week 0 regardless of whether patients had a dose adjustment during the LTE. [b]Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0. [c]Patients who had both stool frequency and rectal bleeding subscores missing at a visit were considered not to be in symptomatic remission for that visit. [d]Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an adverse event of worsening of UC prior to the designated visit were considered not to be in symptomatic remission. [e]Patients who had a missing value in corticosteroid use had their last value carried forward.

- Median CRP concentrations remained low from Weeks 44 to 200 (**Figure 4**)

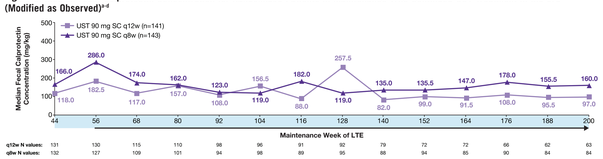
Figure 4. Median CRP Concentration for Randomized Patients in Maintenance Who Continued UST Treatment in the LTE (Modified as Observed)[a-f]



[a]The observed data exclude patients who have missing data and have not had treatment failure (i.e. an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an adverse event of worsening of UC) prior to the designated visit. [b]Includes data from Maintenance Week 0 through Week 200, or up to the time of dose adjustment for patients who had a dose adjustment to UST 90 mg SC q8w (or a sham dose adjustment for the UST 90 mg SC q8w group) during the LTE. [c]Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an adverse event of worsening of UC prior to the designated visit had their Week 0 value of the induction study carried forward to that visit. [d]Patients who have missing data and have not had treatment failure prior to the designated visit are excluded.

- Median fecal calprotectin concentrations remained low from Weeks 44 to 200 (**Figure 5**)

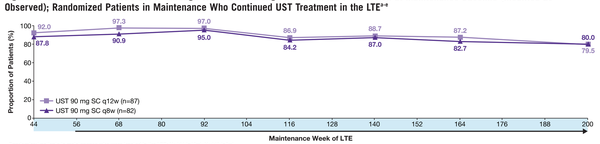
Figure 5. Median Fecal Calprotectin Concentration for Randomized Patients in Maintenance Who Continued UST Treatment in the LTE (Modified as Observed)[a-f]



[a]The observed data exclude patients who have missing data and have not had treatment failure (i.e. an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an adverse event of worsening of UC) prior to the designated visit. [b]Includes data from Maintenance Week 0 through Week 200, or up to the time of dose adjustment for patients who had a dose adjustment to UST 90 mg SC q8w (or a sham dose adjustment for the UST 90 mg SC q8w group) during the LTE. [c]Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an adverse event of worsening of UC prior to the designated visit had their Week 0 value of the induction study carried forward to that visit. [d]The patients who have missing data and have not had treatment failure prior to the designated visit are excluded.

- IBDQ remission was sustained from Weeks 44 to 200 (**Figure 6**)

Figure 6. IBDQ Remission (IBDQ ≥170) Through Week 200 Among Patients in IBDQ Remission at Maintenance Baseline (Modified as Observed); Randomized Patients in Maintenance Who Continued UST Treatment in the LTE[a-e]



[a]The observed data exclude patients who have a missing IBDQ score and have not had treatment failure (i.e. an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an adverse event of worsening of UC) prior to the designated visit. [b]Includes data through Week 200, or up to the time of dose adjustment for patients who had a dose adjustment to UST 90 mg SC q8w (or a sham dose adjustment for the ustekinumab 90 mg SC q8w group) during the LTE. [c]IBDQ remission: total IBDQ score ≥170. [d]Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an adverse event of worsening of UC prior to the designated visit were considered not to be in IBDQ remission. [e]The patients who have a missing IBDQ score and have not had treatment failure prior to the designated visit are excluded from denominator.

Safety

- Among patients who were treated in the LTE, safety events throughout the study were similar among UST-treated patients compared with PBO (**Table 1**)
- During the LTE, the most frequently reported AEs in PBO patients and UST-treated patients were nasopharyngitis, UC worsening, and upper respiratory tract infection (frequency >5 per 100 PYs)
- Overall, 4 patients treated in the LTE reported opportunistic infections (cytomegalovirus infection n=2, *Listeria monocytogenes* n=1, and oral herpes with mouth ulceration and concurrent neutropenia n=1)
- During the LTE, 1 death due to cardiac arrest was reported for a patient who received 1 dose of UST 90 mg SC after dose adjustment from PBO. The patient presented with multiple comorbidities, and the death was deemed by the investigator to be unrelated to UST
- The incidence of antibodies to UST was low through the final safety visit of the LTE (5.5%)

Table 1. Key Safety Events Through 4 Years

	PBO SC[a] (N=188)	UST 90 mg SC q12w[b] (N=141)	UST 90 mg SC q8w[c] (N=380)	UST Combined (N=457)
Avg duration of follow-up (weeks)	83.4	149.4	167.6	185.4
Total patient-years of follow-up	301.7	405.1	1224.5	1629.6
Number of specified events per hundred patient-years of follow-up (95% confidence interval)[d]				
Death	0.00 (0.00, 0.99)	0.00 (0.00, 0.74)	0.08 (0.00, 0.46)	0.06 (0.00, 0.34)
Adverse events	288.04 (269.20, 307.84)	197.72 (184.26, 211.90)	217.56 (209.38, 225.98)	212.63 (205.61, 219.83)
Serious adverse events	10.61 (7.26, 14.97)	6.66 (4.39, 9.70)	7.51 (6.06, 9.21)	7.30 (6.05, 8.74)
Infections[e]	86.18 (76.02, 97.32)	65.66 (58.00, 74.04)	65.01 (60.57, 69.68)	65.17 (61.31, 69.21)
Serious infections[e]	3.31 (1.59, 6.10)	2.47 (1.18, 4.54)	1.88 (1.19, 2.82)	2.03 (1.39, 2.84)
AEs leading to discontinuation of study agent	5.30 (3.03, 8.61)	1.73 (0.69, 3.56)	2.78 (1.92, 3.88)	2.52 (1.81, 3.41)
All malignancies	0.66 (0.08, 2.39)	0.74 (0.15, 2.16)	0.65 (0.28, 1.29)	0.68 (0.34, 1.21)
Excluding nonmelanoma skin cancer	0.33 (0.01, 1.85)	0.00 (0.00, 0.74)	0.16 (0.02, 0.59)	0.12 (0.01, 0.44)
Nonmelanoma skin cancer	0.33 (0.01, 1.85)	0.74 (0.15, 2.16)	0.49 (0.18, 1.07)	0.55 (0.25, 1.05)

[a]Includes 1) data from maintenance Week 8 onward for patients who were in clinical response to UST IV induction dosing and were randomized to PBO SC on entry into the maintenance study, up to the dose adjustment during long-term extension; and 2) data from Week 0 of maintenance for patients who were in clinical response to PBO IV induction dosing and received PBO SC on entry into the maintenance study. [b]Includes data from maintenance Week 0 through final safety visit, or up to the dose adjustment if patients had a dose adjustment during the LTE, for patients who were in clinical response to UST IV induction dosing and were randomized to UST 90 mg SC q12w on entry into the maintenance study. [c]Includes 1) patients who were in clinical response to UST IV induction dosing and were randomized to receive UST 90 mg SC q8w on entry into the maintenance study, with data from maintenance Week 0 through the final safety visit; 2) patients who were in clinical response to UST IV induction dosing, randomized to receive PBO SC or UST 90 mg SC q12w on entry into the maintenance study, and had a dose adjustment to UST SC 90 mg q8w, with data from the time of dose adjustment onward; 3) patients who were not in clinical response to UST at induction Week 8 but were in clinical response at induction Week 16 after a SC administration of UST at induction Week 8 and received UST 90 mg SC q8w on entry into the maintenance study with data from maintenance Week 0 through final safety visit. [d]Confidence intervals based on an exact method assuming that the observed number of events follows a Poisson distribution. [e]Infection as assessed by the investigator.

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1. Sands B, et al. *N Engl J Med.* 2019;381:1201-1214
2. Abreu M, et al. *J Crohns Colitis.* 2022 Mar 3;jjac030. Online ahead of print. https://doi.org/10.1093/ecco-jcc/jjac030

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