STELARA® (ustekinumab) Treatment of Adults with Ulcerative Colitis - UNIFI Study

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UNIFI Overview: Phase 3, randomized, double-blind, placebo-controlled, multicenter, clinical program evaluating the **efficacy and safety of UST** in adults with moderate-to-severe UC (**N=961**).[1]

UNIFI Induction Trial[1]

N=961

Inadequate response to or unacceptable side effects from TNF blockers, vedolizumab, or conventional (ie, nonbiologic) therapy

R 1:1:1

- **UST 130 mg IV** (n=320)
- **UST ~6 mg/kg IV** (n=322)
- **Placebo IV** (n=319)

- **8 weeks single-dose** induction
- Patients **unresponsive to UST IV** received blinded **UST 90 mg SC** and those **unresponsive to placebo** received **UST ~6 mg/kg IV** and were reevaluated at week 16

UNIFI Maintenance Trial[1]

Responders to UST IV **N=523**

R 1:1:1

- **UST 90 mg SC q8w** (n=176)
- **UST 90 mg SC q12w** (n=172)
- **Placebo SC** (n=175)

- **44 weeks** maintenance

UNIFI LTE[2]

- After 44 weeks of maintenance, patients **continued to** receive **UST 90 mg SC q8w** (n=143) or **UST 90 mg SC q12w** (n=141)
- Patients assigned to placebo SC during the maintenance study discontinued after study unblinding

Efficacy: Induction[1]

Significantly higher proportions of patients receiving UST achieved the primary endpoint of **clinical remission**, as well as other efficacy endpoints

Endpoint, Week 8	UST 130 mg IV (n=320)	UST ~6 mg/kg IV (n=322)	Placebo IV (n=319)
Clinical remission	15.6%[a]	15.5%[a]	5.3%
Endoscopic improvement	26.3%[a]	27.0%[a]	13.8%
Clinical response	51.3%[a]	61.8%[a]	31.3%
Change in IBDQ from baseline	31.5[a,b]	31.0[a,b]	10.0
Histologic-endoscopic mucosal healing	20.3%[a]	18.4%[a]	8.9%

[a]*P*<0.001 vs placebo. [b]Multiplicity-controlled for ex-US testing; however, for US testing *P*<0.05, are only nominally significant, as the endpoint is not among the Type 1 error-controlled endpoints (therefore interpret with caution).

Efficacy: Maintenance[1,3]

Significantly greater proportions of patients receiving UST achieved the primary endpoint of **clinical remission.** See other efficacy endpoints below:

Endpoint, Week 44	UST 90 mg SC q8w (n=176)	UST 90 mg SC q12w (n=172)	Placebo SC (n=175)
Clinical remission	43.8%[a]	38.4%[b]	24.0%
Maintenance of clinical response	71.0%[a]	68.0%[a]	44.6%
Corticosteroid-free clinical remission	42.0%[a]	37.8%[b]	23.4%
Maintenance of clinical remission	58%[c] (of n=38)	65%[d] (of n=40)	38% (of n=45)
Endoscopic improvement	51.1%[a]	43.6%[b]	28.6%
Histologic-endoscopic mucosal healing	45.9% (of n=172)	38.8% (of n=170)	24.1% (of n=170)

[a]*P*<0.001, [b]P=0.002, [c]*P*=0.07, [d]*P*=0.01 vs placebo

Safety: Induction and Maintenance[1]

Incidence of **AEs** and **SAEs** in randomized patients:

	UST 130 mg IV (n=321)	UST ~6 mg/kg IV (n=320)	Placebo IV (n=319)
Induction			
≥1 AE	41.4%	50.6%	48.0%
≥1 SAE	3.7%	3.4%	6.9%
Maintenance			
	UST 90 mg SC q8w (n=176)	**UST 90 mg SC q12w (n=172)**	**Placebo SC (n=175)**
≥1 AE	77.3%	69.2%	78.9%
≥1 SAE	8.5%	7.6%	9.7%

Efficacy and Safety: LTE[2,4]

Symptomatic remission through week 92 and safety outcomes through week 96 were reported for the UNIFI LTE for patients who **continued UST SC** maintenance therapy and for the **biologic failure and biologic non-failure subpopulations** (see the Efficacy Results and Safety Results tabs for details)

Clinical remission: total Mayo score of ≤2, with no subscore >1. **Clinical response:** decrease in total Mayo score of ≥30% and of ≥3 points from baseline, with an accompanying decrease of ≥1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1. **Endoscopic improvement:** Mayo endoscopic subscore of 0 or 1. **Histologic-endoscopic mucosal healing:** Mayo endoscopy subscore of 0 or 1 with neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue. **Symptomatic remission:** Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

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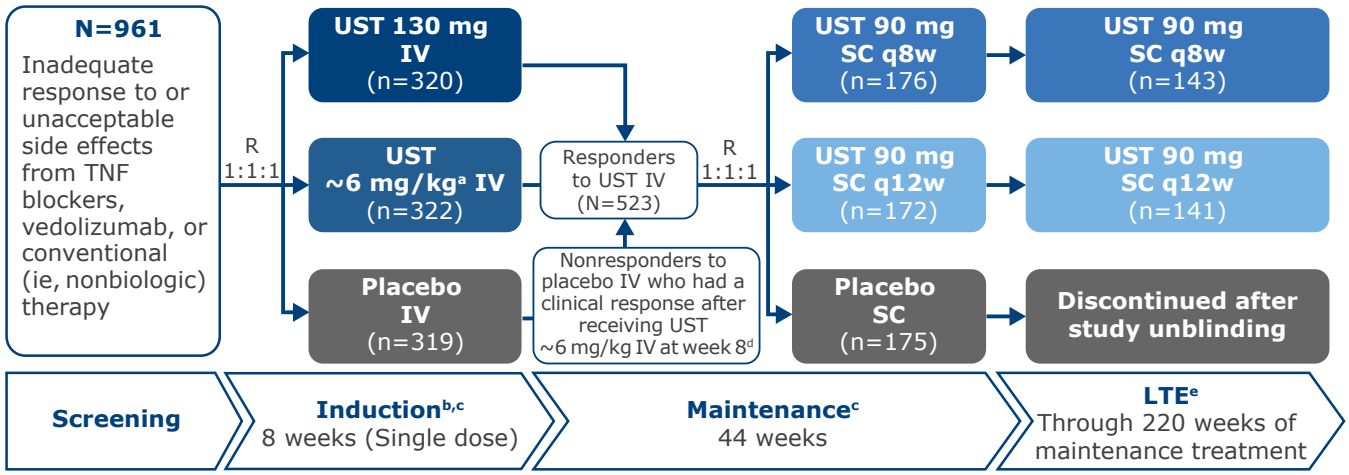
- **UNIFI** (NCT02407236) was a phase 3, randomized, double-blind, placebo-controlled, multicenter clinical program evaluating the efficacy and safety of UST in adult patients with moderate-to-severe UC.[1,2]



[a]Weight range-based UST doses ~6 mg/kg: ≤55 kg, 260 mg; >55 and ≤85 kg, 390 mg; >85 kg, 520 mg.
[b]Patients unresponsive to UST IV induction at week 8 received blinded UST 90 mg SC and reevaluated at week 16.
[c]Stable doses of aminosalicylates and immunomodulators were maintained from baseline of the induction trial through week 44 of the maintenance trial. Oral corticosteroids were maintained at a stable dose during the induction trial and tapered when patients started the maintenance trial.
[d]Patients who did not have a response to IV placebo and who then received an induction dose of UST 6 mg/kg IV at week 8 and had a response at week 16 entered the maintenance trial.
[e]From week 56 onward in the LTE, based on clinical judgment of the investigator, dose adjustment at any time was allowed: patients in the placebo SC arm could receive UST 90 mg SC q8w, patients in the UST 90 mg SC q12w arm could receive UST 90 mg SC q8w, and patients in the UST 90 mg SC q8w arm could continue on UST 90 mg SC q8w (sham dose adjustment).

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Primary Efficacy Endpoint for Induction and Maintenance

- Clinical remission at weeks 8 and 44, respectively[1]

Major Secondary Efficacy Endpoints for Induction and Maintenance

- At week 8:[1]
  - Endoscopic improvement
  - Clinical response
  - Change from baseline in IBDQ score
- At week 44:[1]
  - Maintenance of clinical response through week 44
  - Endoscopic improvement
  - Corticosteroid-free clinical remission
  - Maintenance of clinical remission through week 44 among patients who achieved clinical remission at baseline in the maintenance trial

Additional Induction and Maintenance Efficacy Endpoint

- Histologic-endoscopic mucosal healing at week 8. This endpoint was also evaluated at week 44; however, it was not controlled for multiplicity.[1]

Efficacy Endpoints for the LTE

- Symptomatic remission through week 92[2]
- Symptomatic remission and corticosteroid-free symptomatic remission at week 92[2]
- Median fecal calprotectin levels through week 92[5]

Efficacy Endpoints for the Subgroup Analysis by Biologic Treatment History Status Through 2 Years in the LTE

- Symptomatic remission through week 92[4]
- Symptomatic remission and corticosteroid-free symptomatic remission at week 92[4]

Clinical Endpoint Definitions

Clinical Endpoint Definitions[1,2]

Parameter	Definition
Clinical remission	Total Mayo score of ≤2, with no subscore >1
Clinical response	Decrease in total Mayo score of ≥30% and of ≥3 points from baseline, with an accompanying decrease of ≥1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1
Endoscopic improvement	Mayo endoscopic subscore of 0 or 1
Histologic-endoscopic mucosal healing	Mayo endoscopy subscore of 0 or 1 with neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue
Symptomatic remission	Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0

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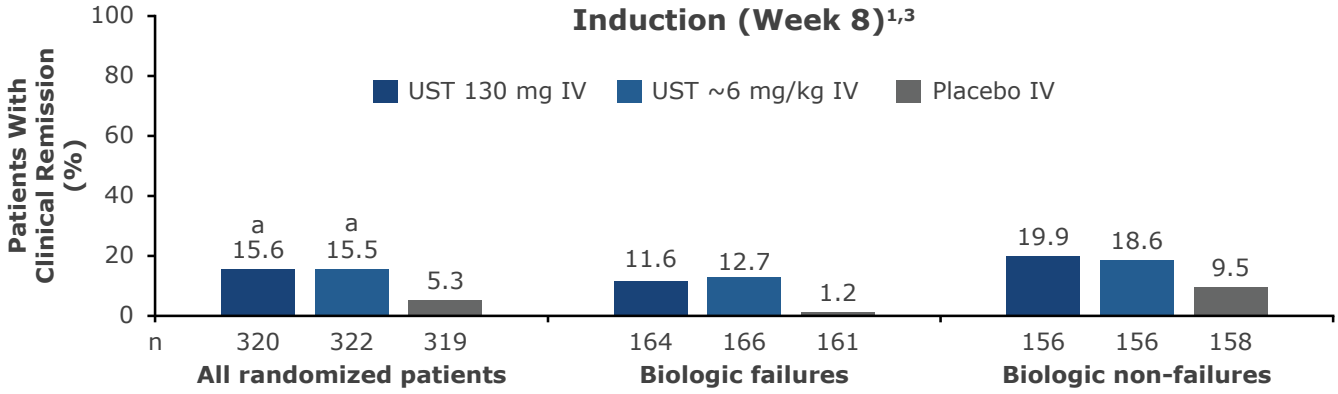
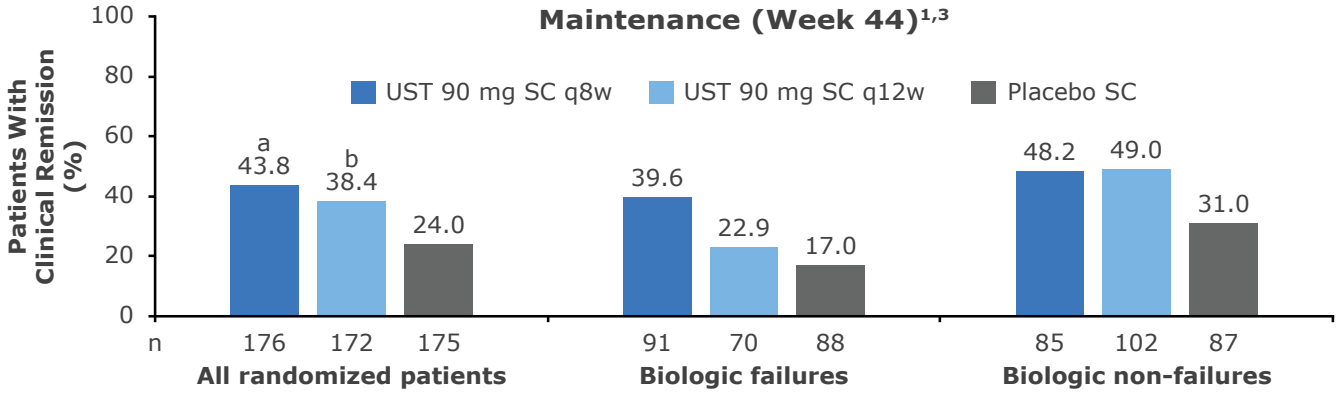
- Overall, 961 patients were randomized to treatment in the primary analysis population (UST 130 mg IV, n=320; UST ~6 mg/kg IV, n=322; placebo IV, n=319).[1]
  - Of these, 912 (94.9%) patients completed the induction trial.
  - Patient characteristics were generally similar across treatment groups.
  - In the induction trial, 491 (51.1%) patients had previous treatment failure with biologic agents.
- At week 8, compared to placebo IV induction, significantly higher proportions of patients receiving UST 130 mg IV and UST ~6 mg/kg IV achieved clinical remission ($P<0.001$).[1]



[a]$P<0.001$ vs placebo.

- At week 44, compared to placebo SC maintenance, significantly higher proportions of patients receiving UST 90 mg SC q8w and UST 90 mg SC q12w achieved clinical remission ($P<0.001$ and $P=0.002$, respectively).[1,3]



[a]$P<0.001$ vs placebo; [b]$P=0.002$ vs placebo.

Clinical remission: total Mayo score of ≤2, with no subscore >1.

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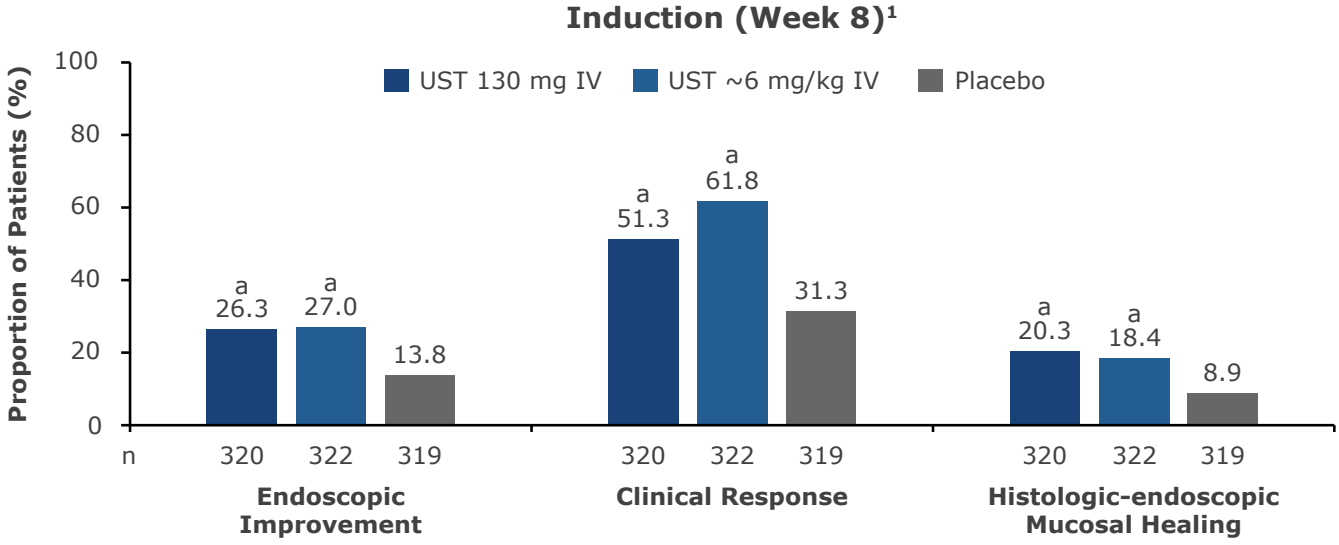
Induction (Week 8)

- Significantly higher proportions of patients in the UST-treated groups (vs placebo) achieved endoscopic improvement, clinical response, histologic-endoscopic mucosal healing, and an improvement from baseline in IBDQ score.[1,3]



[a]*P*<0.001 vs placebo.

Note: Patients who had a prohibited change in concomitant medication for UC or who had undergone an ostomy or colectomy before week 8 were considered not to have met the endpoint.

- At week 8, the median changes from baseline in the IBDQ score were significantly greater in both UST groups than in the placebo group: 31.5 for the UST 130 mg IV group, 31.0 for the UST ~6 mg/kg IV group vs 10.0 for the placebo group (*P*<0.001 for both comparisons with placebo).[3]
  - Multiplicity-controlled for ex-US testing; however, for US testing *P*<0.05, are only nominally significant, as the endpoint is not among the Type 1 error-controlled endpoints (therefore interpret with caution).

Clinical response: decrease in total Mayo score of ≥30% and of ≥3 points from baseline, with an accompanying decrease of ≥1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1. **Endoscopic improvement:** Mayo endoscopic subscore of 0 or 1. **Histologic-endoscopic mucosal healing:** Mayo endoscopy subscore of 0 or 1 with neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue.

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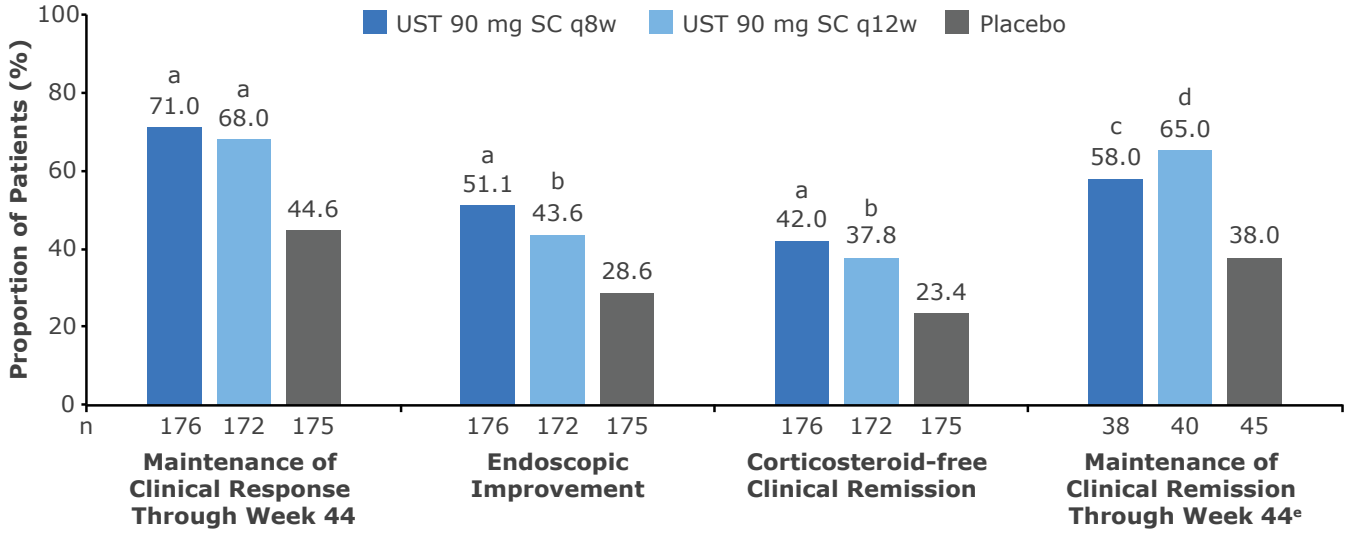
Maintenance (Week 44) – 52 Weeks Post Induction Dose

- Significantly higher proportions of patients receiving UST vs placebo maintained clinical response through week 44, achieved endoscopic improvement, and achieved corticosteroid-free clinical remission.[1,3]

Maintenance (Week 44)[1,3]



[a]*P*<0.001 vs placebo; [b]*P*=0.002 vs placebo; [c]*P*=0.07 vs placebo; [d]*P*=0.01 vs placebo; [e]Among patients in remission at week 0 of maintenance.

- A greater proportion of patients receiving UST vs placebo experienced histologic-endoscopic mucosal healing:[1,3]
  - UST 90 mg SC q8w: 45.9% of 172 patients
  - UST 90 mg SC q12w: 38.8% of 170 patients
  - Placebo SC: 24.1% of 170 patients

Note: Patients who had a prohibited change in medication for UC, had undergone an ostomy or colectomy, or had used a rescue medication after a clinical flare or who had discontinued UST or placebo owing to lack of therapeutic effect or owing to an AE of worsening of UC before the week 44 visit were considered not to have met the dichotomous endpoints or had their value at baseline in the induction trial carried forward from the time of the event onward for continuous endpoints or were considered not to have histologic-endoscopic mucosal healing.

Clinical response: decrease in total Mayo score of ≥30% and of ≥3 points from baseline, with an accompanying decrease of ≥1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1. **Endoscopic improvement:** Mayo endoscopic subscore of 0 or 1. **Histologic-endoscopic mucosal healing:** Mayo endoscopy subscore of 0 or 1 with neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue.

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Additional Analyses of Key Efficacy Endpoints

- Additional analyses of key efficacy endpoints are presented in the following pop-ups:[1,3]

Additional Analyses of Key Efficacy Endpoints: Induction

Additional Analyses of Key Efficacy Endpoints: Maintenance

Early Improvement After IV UST Induction: Analysis of UNIFI Induction Data[6]

- The rapidity of onset of **improvement in patient measures and biologic markers** of UC disease with UST were evaluated.
  - Patients recorded stool frequency and categorized rectal bleeding daily for the 7 days before each visit.
  - Partial Mayo scores were calculated at baseline and post-treatment starting at week 2 using the average of stool frequency and rectal bleeding scores from the most recent consecutive 3-day period before the visit and the PGA score recorded at the visit.
  - As early as week 2, CRP, fecal calprotectin, and fecal lactoferrin were measured at baseline and post-treatment.
  - UST vs placebo comparisons were post-hoc. Nominal P-values were reported.
- By day 7, after IV induction, the mean change from baseline in daily **stool frequency** among patients treated with UST 130 mg IV or UST ~6 mg/kg IV was greater compared with placebo and this trend continued to week 2.
- The proportion of patients **without rectal bleeding** were higher 2 weeks after UST IV induction vs placebo.
- **Partial Mayo scores** in patients who received UST IV induction were improved from baseline after 2 weeks vs placebo ($P<0.001$ for both UST 130 mg and UST ~6 mg/kg IV vs placebo).
- Reductions from baseline **serum CRP concentrations** occurred 2 weeks following UST IV induction ($P<0.001$ for both UST 130 mg IV and UST ~6 mg/kg IV vs placebo).
- Changes from baseline in **fecal calprotectin and fecal lactoferrin** levels were observed at 2 weeks following UST IV induction and at 4 weeks ($P<0.001$ vs placebo for both biomarkers for the UST ~6 mg/kg IV group and $P<0.001$ vs placebo for fecal lactoferrin for the UST 130 mg IV group).

Additional Analyses of Key Efficacy Endpoints: Induction[1,3]

Efficacy Results Comparing Biologic Failures vs Biologic Non-failures

Induction (Week 8)			
Primary efficacy analysis, n	**UST 130 mg IV n=320**	**UST ~6 mg/kg IV n=322**	**Placebo IV n=319**
Patients who are biologic failures, n	164	166	161
Clinical response[a], n (%)	74 (45.1)	95 (57.2)	44 (27.3)
Endoscopic improvement[b], n (%)	30 (18.3)	35 (21.1)	11 (6.8)
Histologic-endoscopic mucosal healing[c], n (%)	22 (13.7)	22 (13.3)	6 (3.7)
Patients who are biologic non-failures, n	156	156	158
Clinical response[a], n (%)	90 (57.7)	104 (66.7)	56 (35.4)
Endoscopic improvement[b], n (%)	54 (34.6)	52 (33.3)	33 (20.9)
Histologic-endoscopic mucosal healing[c], n (%)	42 (27.1)	36 (24.2)	22 (14.2)

[a]A decrease in the total Mayo score of ≥30% and of ≥3 points from baseline, with an accompanying decrease of ≥1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1.

[b]Mayo endoscopic subscore of 0 or 1.

[c]Required both histologic improvement (defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) and endoscopic improvement (Mayo endoscopic subscore of 0 or 1).

Note: Patients who had a prohibited change in concomitant UC medication or an ostomy or colectomy prior to week 8 were considered not to have achieved the dichotomous endpoints for week 8.

IV, intravenous; UC, ulcerative colitis; UST, ustekinumab.

2 weeks following UST IV induction and at 4 weeks (P<0.001 vs placebo for both biomarkers for the UST ~6 mg/kg IV group and P<0.001 vs placebo for fecal lactoferrin for the UST 130 mg IV group).

Additional Analyses of Key Efficacy Endpoints: Maintenance[1,3]

Efficacy Results Comparing Biologic Failures vs Biologic Non-failures

Maintenance (Week 44)			
Primary efficacy analysis, n	**UST 90 mg SC q8w n=176**	**UST 90 mg SC q12w n=172**	**Placebo SC[a] n=175**
Patients who are biologic failures, n	91	70	88
Patients who maintained clinical response through week 44[b], n (%)	59 (64.8)	39 (55.7)	34 (38.6)
Patients who achieved endoscopic improvement at week 44[c], n (%)	41 (45.1)	18 (25.7)	20 (22.7)
Patients in steroid-free clinical remission at week 44[d], n (%)	34 (37.4)	16 (22.9)	14 (15.9)
Patients who maintained remission among remitters at baseline, n (%)	10/20 (50.0)	3/8 (37.5)	8/20 (40.0)
Patients who are biologic non-failures, n	85	102	87
Patients who maintained clinical response through week 44[b], n (%)	66 (77.6)	78 (76.5)	44 (50.6)
Patients who achieved endoscopic improvement at week 44[c], n (%)	49 (57.6)	57 (55.9)	30 (34.5)
Patients in steroid-free clinical remission at week 44[d], n (%)	40 (47.1)	49 (48.0)	27 (31.0)
Patients who maintained remission among remitters at baseline, n (%)	12/18 (66.7)	23/32 (71.9)	9/25 (36.0)

[a]Patients who had a clinical response to UST IV during the induction trial and were randomly assigned to receive placebo SC on entry to the maintenance trial.

[b]Decrease in the total Mayo score of ≥30% and ≥3 points from baseline, with an accompanying decrease of ≥1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1.

[c]Mayo endoscopic subscore of 0 or 1.

[d]Total Mayo score of ≤2 and no subscore >1.

Note: 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 AE of worsening of UC prior to week 44 visit were considered not to have achieved the dichotomous endpoints for week 44.

AE, adverse event; IV, intravenous; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; UC, ulcerative colitis; UST, ustekinumab.

- Details regarding patient discontinuation in the LTE are presented in the following table:

Discontinuation of Study Agent Prior to Week 96[2]

	Randomized Patients Who Continued to Receive Treatment in the LTE			
	UST 90 mg SC q8w	**UST 90 mg SC q12w**	**Placebo SC[a]**	**Total**
Randomized patients treated in the LTE, n	143	141	115	399
Patients who discontinued study agent, n (%)	11 (7.7)	13 (9.2)	47 (40.9)	71 (17.8)
Reasons for discontinuation, n (%)				
AE	2 (1.4)	9 (6.4)	5 (4.3)	16 (4)
Worsening UC	1 (0.7)	6 (4.3)	5 (4.3)	12 (3)
Other than worsening UC	1 (0.7)	3 (2.1)	0	4 (1)
Lack of efficacy	2 (1.4)	1 (0.7)	4 (3.5)	7 (1.8)
Study unblinding	0	0	34 (29.6)	34 (8.5)
Lost to follow-up	0	0	0	0
Not in partial Mayo response 16 weeks following dose adjustment	2 (1.4)	1 (0.7)	1 (0.9)	4 (1)
Death	0	0	0	0
Other	5 (3.5)	2 (1.4)	3 (2.6)	10 (2.5)

[a]Patients who were in clinical response to UST IV induction dosing and were randomized to placebo SC on entry into this maintenance study.

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- Efficacy results through week 92 are presented in the following pop-ups:[2,5]

Symptomatic Remission Through Week 92

Symptomatic Remission and Corticosteroid-Free Symptomatic Remission at Week 92

Median Fecal Calprotectin Levels Through Week 92

Subgroup Analysis by Biologic Treatment History Status in the LTE

- The majority (149/160, 93%) of patients without a history of biologic failure were biologic naïve. Biologic failure to ≥1 biologic was a history of failure to either TNF blockers or vedolizumab.[4]
  - Efficacy results at and through week 92 are presented in the following pop-ups:

Symptomatic Remission Through Week 92

Symptomatic Remission and Corticosteroid-Free Symptomatic Remission at Week 92

Symptomatic Remission Through Week 92[2]

Proportion of Patients (%)	ITT: Dose Adjustment Considered a Treatment Failure (Dose adjustment allowed from Week 56)		ITT: Dose Adjustment Not Considered a Treatment Failure (Dose adjustment allowed from Week 56)			
	Symptomatic Remission[a,b]: Randomized Patients Who Continued to Receive UST in the LTE		Symptomatic Remission[a,c]: Randomized Patients Who Continued to Receive UST in the LTE		Symptomatic Remission[a,d]: Patients Randomized to UST in the Maintenance Study	
	UST 90 mg SC q8w n=143	UST 90 mg SC q12w n=141	UST 90 mg SC q8w n=143	UST 90 mg SC q12w n=141	UST 90 mg SC q8w n=176	UST 90 mg SC q12w n=172
Week 0	69.9	73.8	69.9	73.8	67.6	70.9
Week 4	70.6	73.0	70.6	73.0	68.2	72.1
Week 8	75.5	73.0	75.5	73.0	69.3	71.5
Week 12	83.2	75.9	83.2	75.9	74.4	65.7
Week 16	85.3	79.4	85.3	79.4	76.7	68.0
Week 20	81.8	77.3	81.8	77.3	73.3	64.5
Week 24	82.5	75.9	82.5	75.9	71.0	62.2
Week 28	82.5	79.4	82.5	79.4	72.2	65.7
Week 32	81.8	79.4	81.8	79.4	71.0	63.4
Week 36	82.5	79.4	82.5	79.4	71.0	61.6
Week 40	80.4	79.4	80.4	79.4	68.2	60.5
Week 44	83.2	83.0	83.2	83.0	67.6	62.2
LTE						
Week 56	79.0	81.6	79.0	81.6	66.5	66.9
Week 68	72.0	69.5	82.5	77.3	67.0	63.4
Week 80	71.3	64.5	86.7	74.5	70.5	61.0
Week 92	65.0	65.2	83.2	78.7	67.6	64.5

[a]Symptomatic remission: Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
[b]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. Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an AE of worsening of UC, or were dose adjusted (only occurred from week 56 onward) prior to the designated visit were considered not to be in symptomatic remission.
[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. Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an AE of worsening of UC were considered not to be in symptomatic remission.
[d]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 AE of worsening of UC prior to the week 44 visit were considered not to be in symptomatic remission. Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an AE of worsening of UC after week 44 and prior to the designated visit were considered not to be in symptomatic remission.

AE, adverse event; ITT, intent-to-treat; LTE, long-term extension; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; UC, ulcerative colitis; UST, ustekinumab.

Symptomatic Remission and Corticosteroid-Free Symptomatic Remission at Week 92[2]

ITT: Dose Adjustment Considered a Treatment Failure (Dose Adjustment Allowed From Week 56)		
Proportion of Patients, % (n/N)	**UST 90 mg SC q8w[a]**	**UST 90 mg SC q12w[a]**
Symptomatic remission[b] at week 92	65.0 (93/143)	65.2 (92/141)
Corticosteroid-free symptomatic remission[b] at week 92	64.3 (92/143)	63.8 (90/141)
Corticosteroid-free symptomatic remission[b] at week 92 among patients receiving corticosteroids at maintenance baseline	62.0 (44/71)	57.4 (39/68)

[a]Randomized group at maintenance week 0 regardless of whether patients had a dose adjustment during the LTE. 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. Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an AE of worsening of UC, or were dose adjusted (only occurred from week 56 onward) prior to the designated visit were considered not to be in symptomatic remission.
[b]Symptomatic remission: Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

AE, adverse event; ITT, intent-to-treat; LTE, long-term extension; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; UC, ulcerative colitis; UST, ustekinumab.

Symptomatic Remission Through Week 92

Symptomatic Remission and Corticosteroid-Free Symptomatic Remission at Week 92

Median Fecal Calprotectin Levels Through Week 92[5]

Proportion of Patients[a,b] (%)	Dose Adjustment Allowed From Week 56	
	UST 90 mg SC q8w n=176	UST 90 mg SC q12w n=172
Induction baseline	1510.0	1258.0
Maintenance baseline	450.0	451.0
Week 8	323.5	314.0
Week 24	286.0	286.0
Week 44	218.0	178.0
LTE		
Week 56	306.0	241.5
Week 68	240.0	212.0
Week 80	258.0	212.0
Week 92	201.0	267.0

[a]Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an AE of worsening of UC prior to the week 92 visit had their week 0 value of the induction study carried forward from the time of the event onward.
[b]Patients who had a missing fecal calprotectin value at the designated analysis timepoint had their last value carried forward.

AE, adverse event; LTE, long-term extension; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; UC, ulcerative colitis; UST, ustekinumab.

Symptomatic Remission Through Week 92 by Biologic Treatment History Status[4]

Proportion of Patients (%)	Week	Dose Adjustment Considered a Treatment Failure (Dose Adjustment Allowed From Week 56)		Dose Adjustment Not Considered a Treatment Failure (Dose Adjustment Allowed From Week 56)	
		Symptomatic remission[a,b,c]		Symptomatic remission[a,c,d]	
		UST 90 mg SC q8w n=143	UST 90 mg SC q12w n=141	UST 90 mg SC q8w n=143	UST 90 mg SC q12w n=141
Overall population	Week 0	69.9	73.8	69.9	73.8
	Week 24	82.5	75.9	82.5	75.9
	Week 44	83.2	83.0	83.2	83.0
	LTE				
	Week 56	79.0	81.6	79.0	81.6
	Week 68	72.0	69.5	82.5	77.3
	Week 92	65.0	65.2	83.2	78.7
Biologic naïve patients	Week 0	70.1	78.0	70.1	78.0
	Week 24	86.6	81.7	86.6	81.7
	Week 44	85.1	85.4	85.1	85.4
	LTE				
	Week 56	82.1	82.9	82.1	82.9
	Week 68	80.6	72.0	88.1	78.0
	Week 92	71.6	72.0	86.6	81.7
Biologic failure patients	Week 0	69.0	66.0	69.0	66.0
	Week 24	78.9	66.0	78.9	73.6
	Week 44	80.3	77.4	78.9	69.8
	LTE				
	Week 56	74.6	79.2	74.6	79.2
	Week 68	62.0	64.2	76.1	75.5
	Week 92	56.3	52.8	78.9	73.6

[a]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.
[b]Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an AE of worsening of UC, or were dose adjusted (only occurred from week 56 onward) prior to week 92 were considered not to be in symptomatic remission.
[c]Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
[d]Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an AE of worsening UC were considered not to be in symptomatic remission.

AE, adverse event; LTE, long-term extension; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; UC, ulcerative colitis; UST, ustekinumab.

Symptomatic Remission and Corticosteroid-Free Symptomatic Remission at Week 92 by Biologic Treatment History Status[4]

Proportion of Patients, % (n/N)	UST 90 mg SC q8w	UST 90 mg SC q12w
Dose adjustment considered a treatment failure (dose adjustment allowed from week 56)		
Biologic naïve patients		
Symptomatic remission[a,b]	71.6 (48/67)	72.0 (59/82)
Corticosteroid-free symptomatic remission[a,b,c,d]	70.1 (47/67)	70.7 (58/82)
Biologic failure patients		
Symptomatic remission[a,b]	56.3 (40/71)	52.8 (28/53)
Corticosteroid-free symptomatic remission[a,b,c,d]	56.3 (40/71)	50.9 (27/53)
Dose adjustment not considered a treatment failure (dose adjustment allowed from week 56)		
Biologic naïve patients		
Symptomatic remission[a,e]	86.6 (58/67)	81.7 (67/82)
Corticosteroid-free symptomatic remission[a,c,d,e]	83.6 (56/67)	78.0 (64/82)
Biologic failure patients		
Symptomatic remission[a,e]	78.9 (56/71)	73.6 (39/53)
Corticosteroid-free symptomatic remission[a,c,d,e]	77.5 (55/71)	69.8 (37/53)

[a]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.
[b]Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an AE of worsening UC prior to the designated visit, or were dose adjusted (only occurred from week 56 onward) were considered not to be in symptomatic remission.
[c]Among patients receiving concomitant corticosteroids (including budesonide and beclomethasone dipropionate) at maintenance baseline.
[d]Patients who had a missing value in corticosteroid use at a timepoint had their last available value carried forward to that timepoint.
[e]Patients who had an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect or due to an AE of worsening UC prior to the designated visit were considered not to be in symptomatic remission.

AE, adverse event; q8w, every 8 weeks; q12w, every 12 weeks; SC, subcutaneous; UC, ulcerative colitis; UST, ustekinumab.

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Safety Results in Induction and Maintenance Trials

- Incidence of AEs and SAEs are presented in the following pop-ups.[1]

Safety Results Through the Final Safety Visit in the Induction Trial

Safety Results Through Week 44 in the Maintenance Trial

AEs Through 52 Weeks: UNIFI Induction and Maintenance Trials[1]

- Overall, 2 **deaths** were reported before week 44 in patients who received UST, due to sudden death attributed to esophageal variceal hemorrhage and death from ARDS.
  - There was one death after week 44 in a patient who received UST, with failure to thrive who had a cardiac arrest.
- **Cancer** occurred in 7 out of 825 patients who received UST which included 1 each of prostate, colon, renal papillary, and rectal cancer and 3 NMSCs. Of the 319 patients receiving placebo, one had testicular cancer.
- **Potential opportunistic infections** were reported in 4 patients who received UST and included cytomegalovirus colitis (n=2, during maintenance), *Legionella* pneumonia (n=1, during induction), and concurrent ophthalmic and oral herpes simplex infections (n=1 during maintenance).
- **Major cardiovascular events** included a nonfatal cardiac arrest (n=1, received UST during induction and placebo during maintenance), an acute myocardial infarction (n=1, received UST, died of ARDS complications), and a nonfatal stroke (n=1, received placebo during induction).
- No cases of anaphylaxis or serious hypersensitivity reactions occurred in patients who received UST during induction and maintenance.
- **Antidrug antibodies** occurred in 23 out of 505 patients who received UST during both induction and maintenance.

Safety Results in the LTE

- Safety results are presented in the following pop-ups:[2,4]

Safety Results Among Treated Patients From Week 44 Through Week 96 in the LTE

Safety Results During Maintenance Therapy (Maintenance Week 0 to 96) by Biologic Treatment Status History: Randomized Patients

- In the subgroup analysis by biologic treatment history status in the LTE, malignancy rates were similar among groups from weeks 44 to 96; all occurred in biologic failure patients.[4]

Safety Results Through the Final Safety Visit in the Induction Trial[1]

	Induction[a]				
	Randomly assigned patients			Patients with no response to IV infusion	
	UST 130 mg IV n=321	UST ~6 mg/kg IV n=320	Placebo IV n=319	UST IV → UST 90 mg SC[b] n=233	Placebo IV → UST ~6 mg/kg IV[b] n=184
Average duration of follow-up, weeks	8.6	8.6	8.7	11.5	10.2
Average number of administrations	1.0	1.0	1.0	1.0	1.0
Deaths, n (%)	0	1 (0.3)	0	0	0
Any AE, n (%)	133 (41.4)	162 (50.6)	153 (48.0)	64 (27.5)	55 (29.9)
Common AEs[c], n (%)					
Nasopharyngitis	1 (0.3)	2 (0.6)	1 (0.3)	0	0
UC	9 (2.8)	8 (2.5)	18 (5.6)	20 (8.6)	12 (6.5)
Headache	22 (6.9)	13 (4.1)	14 (4.4)	2 (0.9)	2 (1.1)
Arthralgia	3 (0.9)	6 (1.9)	2 (0.6)	2 (0.9)	1 (0.5)
URTI	6 (1.9)	4 (1.2)	4 (1.3)	5 (2.1)	2 (1.1)
Anemia	7 (2.2)	8 (2.5)	11 (3.4)	1 (0.4)	4 (2.2)
Influenza	2 (0.6)	1 (0.3)	0	2 (0.9)	0
Pyrexia	4 (1.2)	6 (1.9)	6 (1.9)	0	1 (0.5)
SAEs, n (%)	12 (3.7)	11 (3.4)	22 (6.9)	12 (5.2)	7 (3.8)
Infections[d], n (%)	51 (15.9)	51 (15.9)	49 (15.4)	14 (6.0)	22 (12.0)
Serious infections[d], n (%)	2 (0.6)	1 (0.3)	5 (1.6)	2 (0.9)	3 (1.6)
Cancer (excluding NMSC), n (%)	0	0	0	2 (0.9)	0
AEs associated with an infusion or ISR[e], n (%)	7 (2.2)	3 (0.9)	6 (1.9)	6 (2.6)	5 (2.7)

[a]Data through final safety follow-up visit 20 weeks after final dose of UST or placebo for patients who did not enter the maintenance trial.
[b]Data from week 8 onward.
[c]At least 5% of the patients in any group during the maintenance trial.
[d]Assessed by the investigator.
[e]Events that occurred within 1 hour after an infusion during induction.

AE, adverse event; ISR, injection-site reaction; IV, intravenous; NMSC, nonmelanoma skin cancer; SAE, serious AE; SC, subcutaneous; UC, ulcerative colitis; URTI, upper respiratory tract infection; UST, ustekinumab.

Safety Results Through Week 44 in the Maintenance Trial[1]

	Maintenance				
	Randomized population			Nonrandomized population	
	Response to UST IV			Delayed Response to UST	Response to Placebo IV
	UST 90 mg SC q8w n=176	UST 90 mg SC q12w n=172	Placebo SC[a] n=175	UST 90 mg SC q8w n=157	Placebo SC[b] n=103
Average duration of follow-up, weeks	42.2	41.8	42.3	41.8	40.8
Average number of administrations	7.4	7.3	7.1	7.2	6.9
Deaths, n (%)	0	0	0	1 (0.6)	0
Any AE, n (%)	136 (77.3)	119 (69.2)	138 (78.9)	117 (74.5)	79 (76.7)
Common AEs[c], n (%)					
Nasopharyngitis	26 (14.8)	31 (18.0)	28 (16.0)	19 (12.1)	13 (12.6)
UC	18 (10.2)	19 (11.0)	50 (28.6)	26 (16.6)	28 (27.2)
Headache	18 (10.2)	11 (6.4)	7 (4.0)	9 (5.7)	4 (3.9)
Arthralgia	8 (4.5)	15 (8.7)	15 (8.6)	13 (8.3)	9 (8.7)
URTI	16 (9.1)	5 (2.9)	8 (4.6)	7 (4.5)	4 (3.9)
Anemia	7 (4.0)	9 (5.2)	12 (6.9)	9 (5.7)	9 (8.7)
Influenza	10 (5.7)	6 (3.5)	8 (4.6)	7 (4.5)	7 (6.8)
Pyrexia	9 (5.1)	1 (0.6)	7 (4.0)	5 (3.2)	5 (4.9)
SAEs, n (%)	15 (8.5)	13 (7.6)	17 (9.7)	11 (7.0)	8 (7.8)
Infections[d], n (%)	86 (48.9)	58 (33.7)	81 (46.3)	58 (36.9)	44 (42.7)
Serious infections[d], n (%)	3 (1.7)	6 (3.5)	4 (2.3)	2 (1.3)	2 (1.9)
AEs leading to discontinuation of UST or placebo, n (%)	5 (2.8)	9 (5.2)	20 (11.4)	12 (7.6)	13 (12.6)
Cancer (excluding NMSC), n (%)	1 (0.6)	1 (0.6)	0	0	1 (1.0)
AEs associated with an infusion or ISR[e], n (%)	5 (2.8)	1 (0.6)	4 (2.3)	4 (2.5)	0

[a]Patients who had a clinical response to UST IV during induction and were randomly assigned to receive placebo SC on entry to the maintenance trial.
[b]Patients who had a clinical response to placebo IV during induction and received placebo SC on entry to the maintenance trial.
[c]At least 5% of the patients in any group during the maintenance trial.
[d]Assessed by the investigator.
[e]Events that occurred within 1 hour after an infusion during induction.

AE, adverse event; ISR, injection-site reaction; IV, intravenous; NMSC, nonmelanoma skin cancer; q8w, every 8 weeks; q12w, every 12 weeks; SAE, serious AE; SC, subcutaneous; UC, ulcerative colitis; URTI, upper respiratory tract infection; UST, ustekinumab.

Safety Results Among Treated Patients From Week 44 Through Week 96 in the LTE[2]

	UST 90 mg SC q8w n=353	UST 90 mg SC q12w n=141	Combined UST 90 mg SC n=454	Placebo SC[a] n=188
Average duration of follow-up, weeks	45.3	44.5	49.1	37.1
Patients who died, n (%)	1 (0.3)	0	1 (0.2)	0
Patients with ≥1, n (%)				
AEs	242 (68.6)	95 (67.4)	321 (70.7)	125 (66.5)
SAEs	20 (5.7)	7 (5)	27 (5.9)	14 (7.4)
Infections[b]	156 (44.2)	61 (43.3)	213 (46.9)	61 (32.4)
Serious infections[b]	6 (1.7)	4 (2.8)	10 (2.2)	3 (1.6)
AEs leading to discontinuation of study agent	13 (3.7)	6 (4.3)	19 (4.2)	10 (5.3)
All malignancies	2 (0.6)	1 (0.7)	3 (0.7)	2 (1.1)
Excluding NMSC[c]	0	0	0	1 (0.5)
NMSC[d]	2 (0.6)	1 (0.7)	3 (0.7)	1 (0.5)

[a]Patients who were in clinical response to UST IV induction and were randomized to placebo SC on entry into this maintenance study.
[b]Assessed by the investigator.
[c]Lentigo malignant melanoma in situ (placebo only).
[d]Basal cell carcinoma (1 in the placebo group with prior UST induction, 1 in the q12w group, and 2 in the q8w group [1 in the q8w group presented with squamous cell carcinoma]).

AE, adverse event; IV, intravenous; LTE, long-term extension; NMSC, nonmelanoma skin cancer; q8w, every 8 weeks; q12w, every 12 weeks; SAE, serious AE; SC, subcutaneous; UST, ustekinumab.

Safety Results During Maintenance Therapy (Maintenance Week 0 to 96) by Biologic Treatment Status History: Randomized Patients[4]

	With History of Biologic Failure		Biologic Non-failure		Biologic Naïve	
	UST[a] n=191	Placebo[b] n=88	UST[a] n=210	Placebo[c] n=87	UST[a] n=197	Placebo[b] n=84
Average duration of follow-up, weeks	73.72	62.87	81.05	67.47	80.83	68.33
Average duration of treatment, weeks	68.14	52.28	78.06	59.05	77.78	60.31
Patients with ≥1, n (%)						
AEs	175 (91.6)	83 (94.3)	159 (75.7)	69 (79.3)	148 (75.1)	66 (78.6)
SAEs	34 (17.8)	17 (19.3)	13 (6.2)	6 (6.9)	10 (5.1)	5 (6.0)
Infections[d]	132 (69.1)	55 (62.5)	96 (45.7)	41 (47.1)	88 (44.7)	39 (46.4)
AEs leading to discontinuation	20 (10.5)	14 (15.9)	8 (3.8)	9 (10.3)	7 (3.6)	7 (8.3)
Total patient-years of follow-up, n	271	106	327	113	306	110
Event rate per 100 patient-years (number of events)						
AEs	402.55 (1090)	401.31 (427)	237.70 (778)	264.87 (299)	229.25 (702)	254.58 (281)
SAEs	19.57 (53)	20.68 (22)	4.58 (15)	7.97 (9)	3.92 (12)	7.25 (8)
Infections[d]	125.94 (341)	108.08 (115)	73.94 (242)	69.10 (78)	69.89 (214)	68.85 (76)
AEs leading to discontinuation	7.39 (20)	13.16 (14)	2.44 (8)	7.97 (9)	2.29 (7)	6.34 (7)

[a]Includes: 1) data from maintenance week 0 onward for patients who were randomized to receive UST 90 mg SC (q12w or q8w) on entry into this maintenance study; 2) data from the time of dose adjustment onward for patients who had a dose adjustment from placebo SC to UST 90 mg SC q8w.
[b]Includes data from maintenance week 0 onward, or up to the time of dose adjustment to UST 90 mg q8w, for patients who were treated with UST in induction and were crossed over or rerandomized to placebo maintenance.
[c]Includes patients who were biologic naïve as well as those who were biologic experienced (without documented failure).
[d]Assessed by the investigator.

AE, adverse event; q8w, every 8 weeks; q12w, every 12 weeks; SAE, serious AE; SC, subcutaneous; UST, ustekinumab.

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AE	Adverse event	**q12w**	Every 12 weeks
ARDS	Acute respiratory distress syndrome	**R**	Randomization
CRP	C-reactive protein	**SAE**	Serious AE
IBDQ	Inflammatory Bowel Disease Questionnaire	**SC**	Subcutaneous
ISR	Injection-site reaction	**TNF**	Tumor necrosis factor
IV	Intravenous	**UC**	Ulcerative colitis
LTE	Long-term extension	**URTI**	Upper respiratory tract infection
NMSC	Nonmelanoma skin cancer	**US**	United States
PGA	Physician’s Global Assessment	**UST**	Ustekinumab
q8w	Every 8 weeks		

A literature search of Ovid MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File databases (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 01 July 2020.

Summarized in this response are relevant data from the pivotal phase 3 clinical trials (UNIFI) in the treatment of adult patients with moderately to severely active UC. Additional data from beyond these parameters or any additional/available subanalyses from the UNIFI trials not summarized in this response are available upon request.

Thank you for your interest in STELARA® (ustekinumab). The information is presented in response to your unsolicited inquiry. This information is taken from the references cited, but is not intended to serve as a substitute for review of these references. This information is not intended to advocate the use of our product in any manner other than as described in the product monograph. Please refer to the STELARA® Product Monograph available at http://www.janssen.com/canada/products for full prescribing information.

For any questions, please contact Janssen Medical Information at:
1.800.567.3331 or http://www.janssenmedicalinformation.ca

1. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2019;381(13):1201-1214.
2. Sands BE, Sandborn WJ, Panaccione R, et al. Efficacy and saf y of ustekinumab for ulcerative colitis through 2 years: UNIFI long-term extension. Oral presentation presented at: United European Gastroenterology Week (UEGW); October 19-23, 2019; Barcelona, Spain.
3. Sands BE, Sandborn WJ, Panaccione R, et al. Supplement to: Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2019;381(13):1201-1214.
4. Sands BE, Sandborn WJ, Panaccione R, et al. Efficacy of ustekinumab for ulc ative colitis in biologic naïve, biologic non-failure, and biologic failure populations through 2 years: UNIFI long-term extension. Poster presented at: Digestive Disease Week (DDW) 2020; May 2-5, 2020; Virtual Meeting.
5. Sandborn WJ, Sands BE, Panaccione R, et al. Efficacy of ustekinumab for ulc ative colitis through 2 years: results of the UNIFI maintenance study and long-term extension. Poster presented at: Digestive Disease Week (DDW) 2020; May 2-5, 2020; Virtual Meeting.
6. Sands BE, Abreu MT, Marano C, et al. Early improvement after intravenous ustekinumab induction in patients with ulcerative colitis: results from the UNIFI induction trial. Poster presented at: American College of Gastroenterology (ACG); October 25-30, 2019; San Antonio, TX.