Ustekinumab

Stelara®
Interleukin Inhibitor

FORMULATION
Ustekinumab is a fully human IgG1κ monoclonal antibody with an approximate molecular weight of 148600 daltons. Ustekinumab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses. Ustekinumab is prepared from a cell line from murine myeloma origin. No adjuvants are being used.

Ustekinumab (Stelara®) is available in the following presentations:

Solution for injection for subcutaneous administration
Pre-filled Syringe:
- 45 mg/0.5 mL
- 90 mg/mL

Single-use Vial:
- 45 mg/0.5 mL

The solution is clear to slightly opalescent, colorless to light yellow with a pH of approximately 6.0.
The excipients are L-histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80, Sucrose and Water for injection.

Solution for intravenous infusion
Single-use vial:
- 130 mg/26 mL

The solution is clear, colorless to light yellow with a pH of approximately 6.0. The excipients are EDTA disodium salt dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, Polysorbate 80, Sucrose, and Water for Injection.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Mechanism of Action
Ustekinumab (Stelara®) is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab (Stelara®) inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab (Stelara®) cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, Ustekinumab (Stelara®) is not likely to contribute to complement or antibody mediated cytotoxicity of cells expressing IL-12 and/or IL-23 receptors.

IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells. IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype and stimulates interferon gamma (IFNγ) production. IL-23 induces the T helper 17 (Th17) pathway and promotes secretion of IL-17A, IL-21, and IL-22. Levels of IL-12 and IL-23 are elevated in the skin and blood of patients with psoriasis, and serum IL12/23p40 distinguishes patients with psoriatic arthritis from healthy individuals, implicating IL-12 and

IL-23 in the pathophysiology of psoriatic inflammatory diseases. Genetic polymorphisms in IL23A, IL23R, and IL-12B genes confer susceptibility to these disorders. Additionally, IL-12 and IL-23 are highly expressed in lesional psoriatic skin, and IL-12-mediated induction of IFNγ correlates with psoriasis disease activity. IL-23 responsive T-cells have been found in the entheses in a mouse model of inflammatory arthritis, where IL-23 drives entheseal inflammation. In addition, there is pre-clinical evidence implicating IL-23 and downstream pathways in bone erosion and destruction through up-regulation of receptor activator of nuclear factor-κB ligand (RANKL), which activates osteoclasts.

In patients with Crohn's disease, IL-12 and IL-23 are elevated in the intestines and lymph nodes. This is accompanied by increases in serum IFNγ and IL-17A levels, suggesting that IL-12 and IL-23 promote Th1 and Th17 activation in Crohn's disease. Both IL-12 and IL-23 can also stimulate TNFα production by T cells, resulting in chronic intestinal inflammation and epithelial cell injury. Significant associations have been found between Crohn's disease and genetic polymorphisms in the IL23R and IL12B genes, suggesting a potential causal role for IL-12/23 signaling in the disease. This is supported by pre-clinical data demonstrating that IL-12/23 signaling is required for intestinal injury in mouse models of inflammatory bowel disease.

By binding the shared p40 subunit of IL-12 and IL-23, Ustekinumab (Stelara®) may exert its clinical effects in both psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

Pharmacodynamic effects
Treatment with Ustekinumab (Stelara®) resulted in significant improvement in histological measures of psoriasis including epidermal hyperplasia and cell proliferation. These results are consistent with the clinical efficacy observed.

In patients with psoriasis and/or psoriatic arthritis, Ustekinumab (Stelara®) had no apparent effect on the percentages of circulating immune cell populations including memory and naïve T cell subsets or circulating cytokine levels. Systemic markers of inflammation were measurable in the serum at baseline and 4 markers (MDC, VEGF, MCSF-1 and YKL-40) showed modest differences in concentration post-treatment in Ustekinumab (Stelara®)-treated patients as compared to placebo.

Treatment with Ustekinumab (Stelara®) resulted in a decrease in the gene expression of its molecular targets IL-12 and IL-23 as shown by analyses of mRNA obtained from lesional skin biopsies of psoriatic patients at baseline and up to 2 weeks post-treatment. In addition, Ustekinumab (Stelara®) down regulated the gene expression of inflammatory cytokines and chemokines such as MCP-1, TNF-alpha, IP-10, and IL-8 in lesional skin biopsies. These results are consistent with the significant clinical benefit observed with Ustekinumab (Stelara®) treatment in psoriasis.

In psoriasis and psoriatic arthritis studies, clinical response (improvement in PASI or ACR measurements, respectively) appeared to be related to serum ustekinumab levels. Patients with psoriasis with higher PASI response had higher median serum concentrations of ustekinumab than those with lower clinical responses. In psoriasis studies, the proportion of patients who achieved PASI 75 response increased with increasing serum levels of ustekinumab. The proportion of patients who achieved PASI 75 response at Week 28 increased with increasing serum ustekinumab trough levels at Week 28. In psoriatic arthritis studies, patients achieving an ACR 20 response had higher median serum concentrations of ustekinumab than ACR 20 non-responders. The proportion of patients who achieved ACR 20 and ACR 50 response increased with increasing serum levels of ustekinumab.

In patients with Crohn's disease, treatment with Ustekinumab (Stelara®) resulted in a significant decrease in inflammatory markers including C-Reactive Protein (CRP) and fecal calprotectin. Reductions in serum IFNγ and IL-17A, which are IL-12 and IL-23 regulated pro-inflammatory cytokines, were achieved and maintained in Ustekinumab (Stelara®) treated patients through Week 44 compared to placebo. Expression of genes such as IL-12Rβ1 and IL-23 was reduced in inflamed colon tissue from Crohn's disease patients, responders to Ustekinumab (Stelara®) treatment while no significant changes were observed in placebo treated patients at Week 6.

In patients with ulcerative colitis, treatment with Ustekinumab (Stelara®) resulted in a decrease in inflammatory marketers including CRP and fecal calprotectin during the induction phase, which were maintained throughout the maintenance phase and study extension through week 92.

Immunization
During the long-term extension of a Phase 3 psoriasis study (PHOENIX 2), patients treated with Ustekinumab (Stelara®) for at least 3.5 years mounted similar antibody responses to both pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titers were similar among Ustekinumab (Stelara®)-treated and control patients.

Clinical studies
Clinical Efficacy – Plaque Psoriasis (Adults)

The safety and efficacy of Ustekinumab (Stelara®) was assessed in 2 Phase 3, multicenter, randomized, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis (PHOENIX 1 and PHOENIX 2). A total of 1996 patients were enrolled in these studies.

The studies enrolled adults (≥ 18 years) with chronic (> 6 months) plaque psoriasis who had a minimum body surface area (BSA) involvement of 10%, and PASI score ≥ 12 and who were candidates for systemic therapy or phototherapy. Patients with guttate, erythrodermic, or pustular psoriasis were excluded from the studies. No concomitant antipsoriatic therapies were allowed during the study with the exception of low-potency topical corticosteroids on the face and groin after week 12.

The PASI is a composite score that assesses the fraction of body surface area involved with psoriasis and the severity of psoriatic changes within the affected regions (plaque thickness/induration, erythema, and scaling). PASI numeric scores range from 0 to 72, with higher scores representing more severe disease.

Patients achieving ≥ 75% improvement in PASI from baseline (PASI 75) were considered PASI 75 responders. Patients originally randomized to Ustekinumab (Stelara®) who were PASI 75 responders at both Weeks 28 and 40 were considered long-term PASI 75 responders. Patients achieving ≥ 90% improvement in PASI from baseline (PASI 90) were considered PASI 90 responders and patients with ≥ 50% improvement in PASI from baseline (PASI 50) were considered PASI 50 responders. Patients who achieved ≥ 50% but less than 75% improvement in PASI from baseline were considered partial responders. Patients with < 50% improvement in PASI from baseline were considered nonresponders.

Other key efficacy assessments included:

- The Physician's Global Assessment (PGA), a 6-category scale: 0 = cleared, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked and 5 = severe, that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling. The PGA was assessed in PHOENIX 1 and 2.
- The Dermatology Life Quality Index (DLQI), a dermatology-specific quality of life instrument designed to assess the impact of the disease on a patient's quality of life. DLQI scores range from 0 to 30, with a lower score representing a better quality of life. A decrease of 5 in the DLQI score from baseline is considered a clinically meaningful improvement. The DLQI was assessed in PHOENIX 1 and 2.
- The SF-36, a health survey questionnaire consisting of multi-item scales measuring 8 health concepts. The SF-36 yields composite scores that provide a measure of disease impact on physical and mental health status. Higher SF-36 scores indicate a better quality of life. The SF-36 was assessed in PHOENIX 1.
- The Nail Psoriasis Severity Index (NAPSI), a physician-assessed score that measures the severity of nail involvement. The scale consists of 4 components of nail matrix disease and 4 components of nail bed disease with scores from 0 to 8, with a lower scores representing milder disease. The NAPSI was assessed in PHOENIX 1.
- The Hospital Anxiety and Depression Scale (HADS), a self-rating tool developed to evaluate psychological measures in patients with physical ailments. It consists of 2 subscales, one measuring anxiety (A-scale) and one measuring Depression (D-scale), which are scored separately. Lower HADS scores correspond to lesser psychological impairment. The HADS was assessed in PHOENIX 2.
- The Work Limitations Questionnaire (WLQ), a 25-item, self-administered questionnaire that was used to measure the impact of chronic health conditions on job performance and work productivity among employed populations. The WLQ assesses four aspects of work and productivity: Physical Demands, Time Management, Mental-Interpersonal Demand, and Output Demand. The four subscales range from 0-100 with the lower score indicating fewer work limitations. The WLQ was assessed in PHOENIX 2.
- The Itch Visual Analog Scale, used to assess the severity of itch at the time of the assessment. Itch is assessed using a 10 cm horizontal line, or a Visual Analog Scale (VAS), representing the range of itch severity, from 0 (no itch at all) to 10 (severe itch). The Itch VAS was assessed in PHOENIX 1.

PHOENIX 1

PHOENIX 1 evaluated the safety and efficacy of Ustekinumab (Stelara®) versus placebo in 766 patients with plaque psoriasis and the efficacy of every 12 week dosing for patients who were PASI 75 responders.

Patients randomized to Ustekinumab (Stelara®) received 45 mg or 90 mg doses at Weeks 0 and 4 followed by the same doses every 12 weeks. Patients randomized to receive placebo at Weeks 0 and 4 crossed over to receive Ustekinumab (Stelara®) (either 45 mg or 90 mg) at Weeks 12 and 16 followed by the same dose every 12 weeks.

Maintenance dosing (every 12 weeks)

To evaluate the therapeutic benefit of maintenance dosing with Ustekinumab (Stelara®), patients originally randomized to Ustekinumab (Stelara®) who were PASI 75 responders at both Weeks 28 and 40 were re-randomized to either maintenance dosing of Ustekinumab (Stelara®) every 12 weeks or to

placebo (ie, withdrawal of therapy). Patients who were re-randomized to placebo at Week 40 reinitiated Ustekinumab (Stelara®) at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at Week 40.

Dose Adjustment (every 8 weeks)
At Week 28, patients who were nonresponders discontinued treatment and patients who were partial responders were adjusted to every-8-week dosing.

PASI 75 responders at week 28 who became partial responders or nonresponders at Week 40 were adjusted to every-8-week dosing.

All patients were followed for up to 76 weeks following first administration of study treatment.

PHOENIX 2
PHOENIX 2 evaluated the safety and efficacy of Ustekinumab (Stelara®) versus placebo in 1230 patients with plaque psoriasis. Patients randomized to Ustekinumab (Stelara®) received 45 mg or 90 mg doses at Weeks 0 and 4 followed by an additional dose at Week 16. Patients randomized to receive placebo at Weeks 0 and 4 crossed over to receive Ustekinumab (Stelara®) (either 45 mg or 90 mg) at Weeks 12 and 16 followed by the same dose every 12 weeks.

Dose Adjustment (every 8 weeks)
At Week 28, patients who were nonresponders discontinued treatment and patients who were partial responders were re-randomized to continue every-12-week dosing or switch to every-8-week dosing.

PASI 75 responders at week 28 who became partial responders or nonresponders at Week 40 were adjusted to every-8-week dosing.

All patients were followed for up to 52 weeks following first administration of study agent.

Baseline disease characteristics: PHOENIX 1 and 2
Baseline disease characteristics across PHOENIX 1 and 2 were similar (Table 1).

Table 1: Baseline Disease Characteristics

	PHOENIX 1		PHOENIX 2	
	Placebo	Ustekinumab (Stelara®)	Placebo	Ustekinumab (Stelara®)
Patients randomized at Week 0	N= 255	N= 511	N= 410	N= 820
Median BSA	22.0	21.0	20.0	21.0
BSA ≥ 20%	145 (57%)	276 (54%)	217 (53%)	445 (54%)
Median PASI	17.80	17.40	16.90	17.60
PASI ≥ 20	91 (36%)	169 (33%)	133 (32%)	300 (37%)
PGA of marked or severe	112 (44%)	223 (44%)	160 (39%)	328 (40%)
History of psoriatic arthritis	90 (35%)	168 (33%)	105 (26%)	200 (24%)
Prior phototherapy	150 (59%)	342 (67%)	276 (67%)	553 (67%)
Prior conventional systemic therapy excluding biologics	142 (56%)	282 (55%)	241 (59%)	447 (55%)
Prior conventional systemic or biologic therapy	189 (74%)	364 (71%)	287 (70%)	536 (65%)
Failed to respond to, had contraindication for, or intolerant to ≥ 1 conventional therapy	139 (55%)	270 (53%)	254 (62%)	490 (60%)
Failed to respond to, had contraindication for, or intolerant to ≥ 3 conventional therapies	30 (12%)	54 (11%)	66 (16%)	134 (16%)

Efficacy at the Primary Endpoint, PHOENIX 1 and 2

In both the PHOENIX 1 and PHOENIX 2 studies, a significantly greater proportion of patients randomized to treatment with Ustekinumab (Stelara®) were PASI 75 responders compared with placebo at Week 12 (Table 2). In the PHOENIX 1 study, 67% and 66% of patients receiving Ustekinumab (Stelara®) 45 mg and 90 mg, respectively, achieved a PASI 75 response at Week 12 compared with 3% of patients receiving placebo. In the PHOENIX 2 study, 67% and 76% of patients receiving Ustekinumab (Stelara®) 45 mg and 90 mg respectively achieved a PASI 75 response at Week 12 compared with 4% of patients receiving placebo.

All 3 components of the PASI (plaque thickness/induration, erythema, and scaling) contributed comparably to the improvement in PASI.

The efficacy of Ustekinumab (Stelara®) was significantly superior ($p<0.001$) to placebo across all subgroups defined by baseline demographics, clinical disease characteristics (including patients with a history of psoriatic arthritis) and prior medication usage. While pharmacokinetic modeling suggested a trend towards higher CL/F in patients with diabetes, a consistent effect on efficacy was not observed.

Other efficacy measures at Week 12

In both PHOENIX 1 and PHOENIX 2, compared with placebo, significantly greater proportions of patients randomized to 45 mg or 90 mg Ustekinumab (Stelara®) achieved a cleared or minimal PGA score, and significantly greater proportions of patients randomized to 45 mg or 90 mg Ustekinumab (Stelara®) were PASI 90 and PASI 50 responders at Week 12 (Table 2). In the PHOENIX 1 study, 59% and 61% of the

patients treated with 45 mg and 90 mg Ustekinumab (Stelara®), respectively, achieved PGA scores of cleared or minimal compared with 4% of placebo-treated patients. In PHOENIX 2, 68% and 73% of patients receiving 45 mg or 90 mg Ustekinumab (Stelara®), respectively, had cleared or minimal PGA scores compared with 4% of the placebo patients. In PHOENIX 1, PASI 90 was achieved by 42% and 37% of the patients treated with 45 mg and 90 mg Ustekinumab (Stelara®), respectively, compared with 2% of placebo-treated patients. In PHOENIX 2, the percentage of patients achieving PASI 90 was 42% in the 45 mg Ustekinumab (Stelara®) group, 51% in the 90 mg Ustekinumab (Stelara®) group and 1% in the placebo group. The percentage of patients achieving PASI 50 in PHOENIX 1 was 84% and 86% in the 45 mg and 90 mg Ustekinumab (Stelara®) groups, respectively, compared with 10% in the placebo group. Similarly, 84% of patients treated with 45 mg Ustekinumab (Stelara®), 89% of patients treated with 90 mg Ustekinumab (Stelara®) and 10% of patients treated with placebo reached PASI 50 in PHOENIX 2 (Table 2).

Table 2: Key psoriasis endpoints– PHOENIX 1 and PHOENIX 2

Week 12

	PHOENIX 1			PHOENIX 2		
		Ustekinumab (Stelara®)			Ustekinumab (Stelara®)	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Patients randomized at Week 0	255	255	256	410	409	411
PASI response						
PASI 50 response [a]	26 (10%)	213 (84%)	220 (86%)	41 (10%)	342 (84%)	367 (89%)
PASI 75 response [a]	8 (3%)	171 (67%)	170 (66%)	15 (4%)	273 (67%)	311 (76%)
PASI 90 response [a]	5 (2%)	106 (42%)	94 (37%)	3 (1%)	173 (42%)	209 (51%)
PGA of Cleared or Minimal [a,b]	10 (4%)	151 (59%)	156 (61%)	18 (4%)	277 (68%)	300 (73%)
PASI 75 response by weight						
≤ 100 kg						
N	166	168	164	290	297	289
PASI 75 response	6 (4%)	124 (74%)	107 (65%)	12 (4%)	218 (73%)	225 (78%)
>100 kg						
N	89	87	92	120	112	121
PASI 75 response	2 (2%)	47 (54%)	63 (68%)	3 (3%)	55 (49%)	86 (71%)
PGA of Cleared or Minimal by weight						
≤ 100 kg						
N	166	168	164	290	297	289
PGA response [b]	7 (4%)	108 (64%)	103 (63%)	14 (5%)	220 (74%)	216 (75%)
>100 kg						
N	89	87	92	120	112	121
PGA response [b]	3 (3%)	43 (49%)	53 (58%)	4 (3%)	57 (51%)	84 (69%)

Week 28				
	PHOENIX 1		PHOENIX 2	
	Ustekinumab (Stelara®)		Ustekinumab (Stelara®)	
	45 mg	90 mg	45 mg	90 mg
N	250	243	397	400
PASI response				
PASI 50 response	228 (91%)	234 (96%)	369 (93%)	380 (95%)
PASI 75 response	178 (71%)	191 (79%)	276 (70%)	314 (79%)
PASI 90 response	123 (49%)	135 (56%)	178 (45%)	217 (54%)
PGA of Cleared or Minimal[b]-	146 (58%)	160 (66%)	241 (61%)	279 (70%)
PASI 75 response by weight				
≤ 100 kg				
N	164	153	287	280
PASI 75 response	130 (79%)	124 (81%)	217 (76%)	226 (81%)
>100 kg				
N	86	90	110	119
PASI 75 response	48 (56%)	67 (74%)	59 (54%)	88 (74%)
PGA of Cleared or Minimal by weight				
≤ 100 kg				
N	164	153	287	280
PGA response[b]	106 (65%)	106 (69%)	192 (67%)	207 (74%)
>100 kg				
N	86	90	110	119
PGA response	40 (47%)	54 (60%)	49 (45%)	71 (60%)

[a] $p < 0.001$ for 45 mg or 90 mg comparison with placebo.
[b] data corrected post EMEA inspection

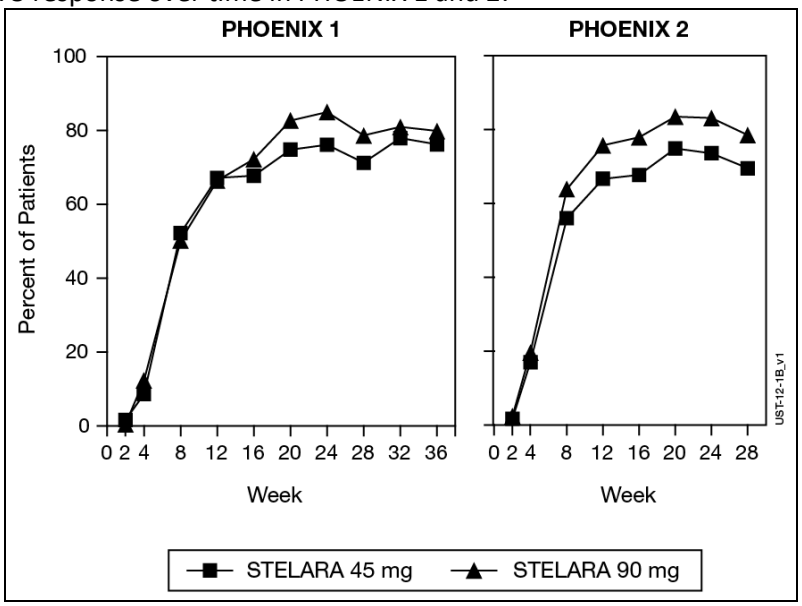
Response over time

In PHOENIX 1, significantly greater proportions of Ustekinumab (Stelara®)-treated patients had PASI 50 responses (9% and 10% for the 45 mg and 90 mg groups, respectively) compared with placebo (2%) by Week 2 ($p< 0.001$). Significantly greater proportions of patients treated with Ustekinumab (Stelara®) achieved PASI 75 responses (9% and 12% for the 45 mg and 90 mg Ustekinumab (Stelara®) groups, respectively) compared with placebo (0.4%) by Week 4 ($p< 0.001$). Maximum response was generally achieved by Week 24 in the 45 mg and 90 mg-Ustekinumab (Stelara®) treatment groups, and response rates were generally sustained through Week 36 (Figure 1). In PHOENIX 1, PASI 75 rates at Week 24 were 76% for the 45 mg group, and 85% for the 90 mg group. Higher response rates were observed in patients receiving Ustekinumab (Stelara®) 90 mg than in those receiving Ustekinumab (Stelara®) 45 mg by Week 16 and these higher response rates were sustained through Week 36 (Figure 1). Similar results were observed in the PHOENIX 2 study through Week 28.

In pre-specified analyses of efficacy by body weight in PHOENIX 1 and PHOENIX 2, no consistent pattern of dose response was seen in patients ≤ 100 kg. In patients who weighed >100 kg, higher PASI 75

response rates were seen with 90 mg dosing compared with 45 mg dosing, and a higher proportion of patients receiving 90 mg dosing had PGA scores of cleared or minimal compared with patients receiving 45 mg dosing (Table 2).

Figure 1: PASI 75 response over time in PHOENIX 1 and 2:



Therapeutic benefit of Long-term continuous use

At Week 40 in PHOENIX 1, 162 patients were randomized to receive Ustekinumab (Stelara®) (maintenance) and 160 were randomized to receive placebo (treatment withdrawal). Maintenance of PASI 75 was significantly superior with continuous treatment compared with treatment withdrawal ($p<0.001$). Similar results were seen with each dose of Ustekinumab (Stelara®) (Figure 2). At 1 year (Week 52), 89% of patients re-randomized to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomized to placebo (treatment withdrawal) ($p<0.001$). At 18 months (Week 76), 84% of patients re-randomized to maintenance treatment were PASI 75 responders compared with 19% of patients re-randomized to placebo (treatment withdrawal). At 3 years (Week 148), 82% of patients re-randomized to maintenance treatment were PASI 75 responders. At 5 years (Week 244), 80% of patients re-randomized to maintenance treatment were PASI 75 responders.

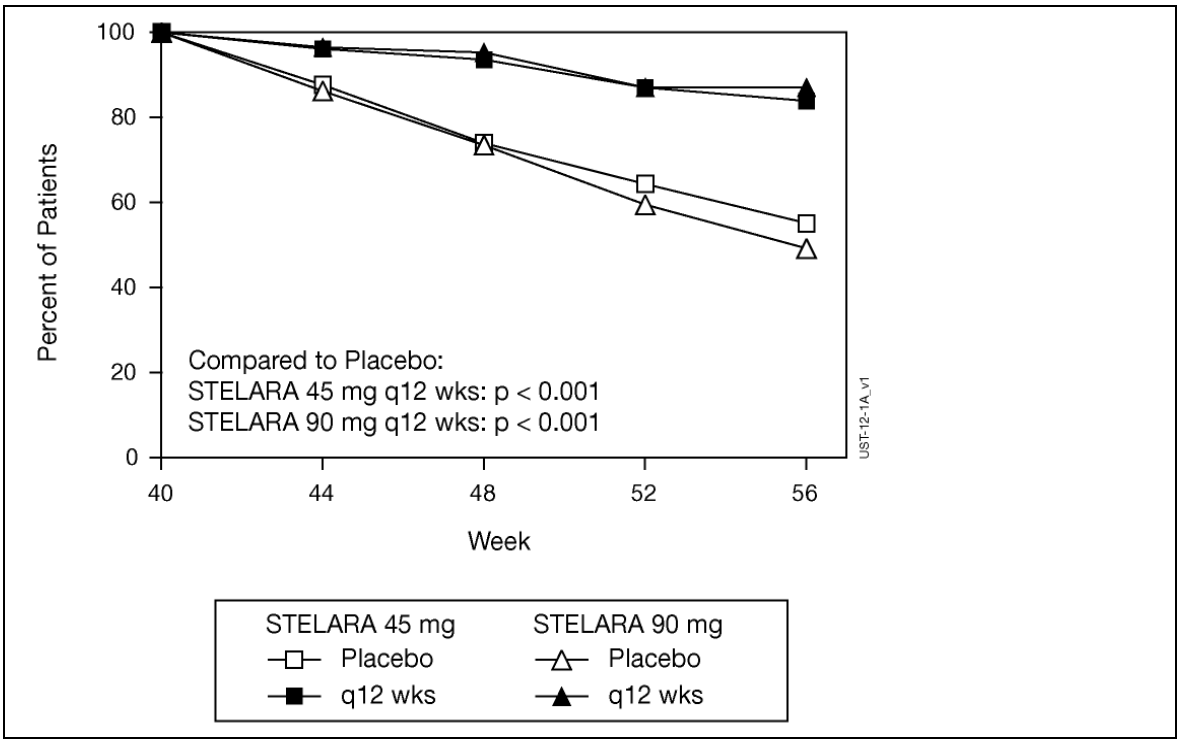


Figure 2 Life-table estimate of percent of patients maintaining PASI 75 response; patients randomized at Week 40 (PHOENIX 1)

Efficacy of retreatment

In PHOENIX 1, after withdrawal from therapy, patients reinitiated their original Ustekinumab (Stelara®) treatment regimen after loss of ≥ 50% of PASI improvement. Retreatment with Ustekinumab (Stelara®) resulted in 71% of evaluated patients regaining PASI 75 response within 8 weeks after reinitiating therapy and 85% of evaluated patients regaining PASI 75 response within 12 weeks after reinitiating therapy.

Dosing Interval Adjustment

In PHOENIX 1, Week 28 and Week 40 Partial Responders and Week 40 Nonresponders were adjusted from every 12 week to every 8 week dosing. Approximately 40%-50% of Week 28 Partial Responders to every 12 week dosing achieved PASI 75 response after adjustment to every 8 week dosing and this proportion of PASI 75 responders was maintained through Week 52. A similar proportion of patients who were PASI 75 responders at Week 28 and subsequently became partial responders or nonresponders at Week 40 achieved PASI 75 response following a dosing interval adjustment to every 8 weeks.

Quality of Life

In PHOENIX 1 and 2, the mean baseline DLQI scores ranged from 11 to 12. In PHOENIX 1, the mean baseline SF-36 Physical Component ranged from 47-49 and the mean baseline SF-36 Mental Component was approximately 50. Quality of life improved significantly in patients randomized to 45 mg or 90 mg Ustekinumab (Stelara®) compared with patients randomized to placebo as evaluated by DLQI in PHOENIX 1 and 2 and SF-36 in PHOENIX 1 (Tables 3 and 4). Quality of life improvements were significant as early as 2 weeks in patients treated with Ustekinumab (Stelara®) and these improvements were maintained over time with continued dosing.

Table 3: Quality of Life endpoints through Week 40 – PHOENIX 1

		Ustekinumab (Stelara®)	
	Placebo	45 mg	90 mg
Patients randomized at Week 0	255	255	256
DLQI			
Baseline			
N	254	255	255
Mean ± SD	11.8 ± 7.41	11.1 ± 7.09	11.6 ± 6.92
Median	10.0	10.0	11.0
Change from baseline			
Week 2[a]			
N	253	255	254
Mean ± SD	-0.9 ± 4.88	-3.6 ± 4.51	-4.5 ± 5.31
Median	-1.0	-3.0	-4.0
Week 12[a]			
N	252	254	249
Mean ± SD	-0.6 ± 5.97	-8.0 ± 6.87	-8.7 ± 6.47
Median	0.0	-6.0	-7.0
Week 28			
N	NA	249	241
Mean ± SD	NA	-8.1 ± 7.23	-9.6 ± 7.17
Median	NA	-7.0	-8.0
Week 40			
N	NA	246	236
Mean ± SD	NA	-8.2 ± 7.23	-9.5 ± 6.96
Median	NA	-7.0	-9.0
SF-36			
Physical component summary			
Baseline			
N	254	255	255
Mean ± SD	47.22 ± 10.240	48.90 ± 9.555	47.51 ± 9.224
Median	50.70	51.60	49.60
Change from Baseline			
Week 12[a]			
N	250	255	249
Mean ± SD	-0.53 ± 7.457	1.97 ± 7.422	3.23 ± 7.590
Median	-0.25	1.30	1.50

Week 28			
N	NA	250	239
Mean ± SD	NA	1.86 ± 8.301	3.17 ± 7.855
Median	NA	1.00	1.90
Week 40			
N	NA	246	236
Mean ± SD	NA	1.77 ± 8.402	2.96 ± 8.027
Median	NA	0.80	2.10
Mental component summary			
Baseline			
N	254	255	255
Mean ± SD	49.62 ± 10.582	50.02 ± 10.425	49.86 ± 10.175
Median	53.35	52.90	53.10
Change from Baseline			
Week 12[a]			
N	250	255	249
Mean ± SD	-1.33 ± 7.473	2.12 ± 9.308	2.54 ± 9.506
Median	-0.60	0.80	1.50
Week 28			
N	NA	250	239
Mean ± SD	NA	1.80 ± 9.578	3.47 ± 9.587
Median	NA	0.40	1.50
Week 40			
N	NA	246	236
Mean ± SD	NA	2.17 ± 9.137	2.91 ± 9.418
Median	NA	0.95	1.10

[a] $p < 0.001$ for 45 mg or 90 mg comparison with placebo.
NA = not applicable

Table 4: Quality of Life endpoints through Week 24 – PHOENIX 2

		Ustekinumab (Stelara®)	
	Placebo	45 mg	90 mg
Patients randomized at Week 0	410	409	411
DLQI			
Baseline			
N	408	406	408
Mean ± SD	12.3 ± 6.86	12.2 ± 7.07	12.6 ± 7.29
Median	11.0	12.0	12.0
Change from baseline			
Week 4[a]			
N	405	404	404
Mean ± SD	-1.4 ± 4.68	-6.9 ± 6.07	-7.0 ± 5.86
Median	-1.0	-6.0	-6.0
Week 12[a]			
N	400	401	402
Mean ± SD	-0.5 ± 5.66	-9.3 ± 7.12	-10.0 ± 6.67
Median	-0.5	-8.0	-9.0
Week 24			

Table 4: Quality of Life endpoints through Week 24 – PHOENIX 2

		Ustekinumab (Stelara®)	
	Placebo	45 mg	90 mg
N	NA	394	399
Mean ± SD	NA	-9.5 ± 7.26	-10.3 ± 6.96
Median	NA	-8.0	-9.0

[a] p < 0.001 for 45 mg or 90 mg comparison with placebo.
NA=not applicable

Nail Psoriasis

In PHOENIX 1, the median baseline NAPSI score for nail psoriasis was 4.0 and the median number of fingernails involved with psoriasis was 8.0. Nail psoriasis improved significantly in patients randomized to 45 mg or 90 mg Ustekinumab (Stelara®) compared with patients randomized to placebo when measured by the NAPSI score (Tables 5 and 6). Nail psoriasis continued to improve over time through Week 52 in patients treated with Ustekinumab (Stelara®).

Table 5: Summary of percent improvement from baseline in NAPSI at Week 12; patients randomized at Week 0 with nail psoriasis present at Week 0 - PHOENIX 1

		Ustekinumab (Stelara®)	
	Placebo	45 mg	90 mg
Patients randomized at Week 0 with nail psoriasis present at Week 0	176	182	187
Week 12 [a]			
N	174	182	184
Mean ± SD	11.8 ± 51.09	26.7 ± 56.80	24.9 ± 48.90
Median	0.0	25.0	25.0

[a] p ≤ 0.001 for 45 mg or 90 mg comparison with placebo.

Table 6: Summary of percent improvement from baseline in NAPSI at Week 24; patients randomized at Week 0 with nail psoriasis present at Week 0 - PHOENIX 1

			Ustekinumab (Stelara®)	
	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg
Patients randomized at Week 0 with nail psoriasis present at Week 0	93	83	182	187
Week 24				
N	89	77	179	181
Mean ± SD	29.1 ± 60.83	40.5 ± 43.37	46.5 ± 47.41	48.7 ± 45.58
Median	33.3	42.9	50.0	50.0

Hospital Anxiety and Depression Scale

At baseline in PHOENIX 2, the mean HADS anxiety and depression scores were 6.9 and 5.1, respectively. Both anxiety and depression scores were reduced significantly in patients randomized to 45 mg or 90 mg Ustekinumab (Stelara®) at Week 12 compared with patients randomized to placebo (Table 7). HADS improvements were maintained through Week 24 (Table 8).

Table 7: Summary of change from baseline in Hospital Anxiety and Depression at Week 12; patients randomized at Week 0 - PHOENIX 2

		Ustekinumab (Stelara®)	
	Placebo	45 mg	90 mg
Patients randomized at Week 0	410	409	411
Anxiety score [a]			
N	395	399	399
Mean ± SD	-0.11 ± 2.689	-1.59 ± 3.570	-1.60 ± 3.351
Median	0.00	-1.00	-1.00
Depression score [a]			
N	398	399	401
Mean ± SD	0.21 ± 2.757	-1.71 ± 3.124	-2.06 ± 3.420
Median	0.00	-1.00	-1.00

[a] $p < 0.001$ for 45 mg or 90 mg comparison with placebo.

Table 8: Summary of change from baseline in Hospital Anxiety and Depression at Week 24; patients randomized at Week 0 – PHOENIX 2

	Ustekinumab (Stelara®)			
	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg
Patients randomized at Week 0	205	205	409	411
Anxiety score				
N	183	191	393	395
Mean ± SD	-1.52 ± 3.148	-1.76 ± 3.245	-1.80 ± 3.725	-1.99 ± 3.463
Median	-1.00	-1.00	-1.00	-1.00
Depression score				
N	184	190	391	398
Mean ± SD	-1.65 ± 3.207	-1.42 ± 3.013	-1.77 ± 3.449	-2.26 ± 3.490
Median	-1.00	-1.00	-1.00	-2.00

Work Limitations Questionnaire

The Work Limitations Questionnaire obtained at baseline showed impaired work productivity among patients with psoriasis evaluated in PHOENIX 2 for the Physical Demands, Time Management, Mental-Interpersonal and Output Demands component scores. Work productivity improved significantly more in patients randomized to Ustekinumab (Stelara®) at Week 12 compared with patients randomized to placebo as measured by the four WLQ subscales (Physical Demands, Time Management, Mental-Interpersonal, and Output Demands; Table 9).

Table 9: Summary of change from baseline in Work Limitations Questionnaire at Week 12; patients randomized at Week 0 – PHOENIX 2

		Ustekinumab (Stelara®)	
	Placebo	45 mg	90 mg
Patients randomized at Week 0	410	409	411
Physical Demands score [a]			
N	277	277	281
Mean ± SD	-0.20 ± 30.991	-7.61 ± 30.917	-5.05 ± 34.050
Median	0.00	0.00	0.00

Time Management score [b]			
N	259	255	265
Mean ± SD	0.74 ± 18.962	-6.58 ± 21.634	-9.06 ± 24.239
Median	0.00	-5.00	-3.30
Mental - Interpersonal score [b]			
N	272	275	276
Mean ± SD	1.11 ± 18.881	-7.82 ± 22.684	-7.51 ± 19.366
Median	0.00	-2.80	-1.35
Output Demands score [b]			
N	276	274	279
Mean ± SD	1.08 ± 16.062	-6.82 ± 22.367	-6.98 ± 20.866
Median	0.00	0.00	0.00

[a] p = 0.001 and 0.060 for the 45 mg and 90 mg comparisons, respectively, with placebo
[b] p < 0.001 for 45 mg or 90 mg comparison with placebo

Itch VAS

Itch associated with psoriasis improved significantly (p<0.001) at Week 12 in patients randomized to 45 mg or 90 mg Ustekinumab (Stelara®) compared with patients randomized to placebo as evaluated by Itch VAS in PHOENIX 1 (Table 10).

Table 10: Summary of change from baseline in itch VAS at Week 12; patients randomized at Week 0 – PHOENIX 1

		Ustekinumab (Stelara®)	
	Placebo	45 mg	90 mg
Patients randomized at Week 0	255	255	256
Week 12 [a]			
N	252	253	249
Mean ± SD	-0.78 ± 2.538	-4.91 ± 3.142	-5.14 ± 3.020
Median	-0.30	-5.50	-5.50

[a] p < 0.001 for 45 mg or 90 mg comparison with placebo.

ACCEPT

In addition, a multicenter, randomized, single-blind, active-controlled study (ACCEPT) compared the safety and efficacy of ustekinumab and etanercept in patients 18 years of age and older with chronic (>6 months) plaque psoriasis who had a minimum BSA involvement of 10%, PASI score ≥12, Physician Global Assessment (PGA) score ≥ 3, who were candidates for phototherapy or systemic therapy, and who had had an inadequate response to, intolerance to, or contraindication to cyclosporine, MTX, or PUVA therapy. A total of 903 patients were enrolled in the study.

The ACCEPT trial compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept in patients with moderate to severe psoriasis. The active-controlled portion of the study was from Week 0 to Week 12, during which patients were randomized to receive etanercept (50 mg twice a week) ustekinumab 45 mg at Weeks 0 and 4, or ustekinumab 90 mg at Weeks 0 and 4. This trial was powered to test the superiority of each ustekinumab dose to etanercept on the primary endpoint of the proportion of patients who achieved a PASI 75 at week 12.

Significantly greater proportions of subjects treated with ustekinumab 45 mg (67%; p = 0.012) or 90 mg (74%; p < 0.001) were PASI 75 responders at Week 12 compared with the etanercept group (57%). PASI

90 response was observed in 36% and 45 % of patients in the ustekinumab 45 mg and 90 mg groups, respectively, compared with 23% of patients receiving etanercept (p<0.001 for each comparison versus etanercept). PASI 100 response was observed in 12% and 21% of patients in the ustekinumab 45 mg and 90 mg groups, respectively, compared to 6% of patients receiving etanercept (Table 11). In addition, a greater proportion of patients in the ustekinumab 45 mg and 90 mg treatment groups achieved a PGA score of "cleared" or "minimal" (65% and 71%, respectively) compared with patients in the etanercept treatment group (49%) (p<0.001 for each comparison versus etanercept).

In pre-specified analyses of efficacy by body weight in ACCEPT, minimal dose response to ustekinumab was evident in patients ≤ 100 kg. In patients who weighed >100 kg, higher PASI 75 response rates were seen with 90 mg dosing compared with 45 mg dosing, and a higher proportion of patients receiving 90 mg dosing had PGA scores of cleared or minimal compared with patients receiving 45 mg dosing (Table 11).

Table 11: Key psoriasis endpoints at Week 12: ACCEPT

	ACCEPT		
	Etanercept (50 mg twice a week)	Ustekinumab (week 0 and week 4)	
		45 mg	90 mg
Patients randomized	347	209	347
PASI RESPONSE			
PASI 50 response	286 (82%)	181 (87%)	320 (92%)[a]
PASI 75 response	197 (57%)	141 (67%)[b]	256 (74%)[a]
PASI 90 response	80 (23%)	76 (36%)[a]	155 (45%)[a]
PASI 100 response	22 (6%)	25 (12%)[c]	74 (21%)[a]
PGA of Cleared or Minimal	170 (49%)	136 (65%)[a]	245 (71%)[a]
PASI 75 RESPONSE BY WEIGHT			
≤ 100 kg			
N	251	151	244
PASI 75 response	154 (61%)	109 (72%)	189 (77%)
>100 kg			
N	96	58	103
PASI 75 response	43 (45%)	32 (55%)	67 (65%)
PGA OF CLEARED OR MINIMAL BY WEIGHT			
≤ 100 kg			
N	251	151	244
PGA response	131 (52%)	110 (73%)	185 (76%)
>100 kg			
N	96	58	103
PGA response	39 (41%)	26 (45%)	60 (58%)
PASI 75 RESPONSE BY NUMBER OF UNSUITABLE			

CONVENTIONAL SYSTEMIC AGENTS [g]			
-at least one therapy			
N	347	209	346
PASI 75 Response	197 (57%)	141 (67%) [b]	256 (74%) [a]
-at least two therapies			
N	186	118	185
PASI 75 Response	94 (51%)	79 (67%) [d]	137 (74%) [a]
-at least three therapies			
N	52	31	47
PASI 75 Response	20 (38%)	17 (55%) [e]	34 (72%) [f]

[a] p <0.001 for ustekinumab 45 mg or 90 mg comparison with etanercept.
[b] p =0.012 for ustekinumab 45 mg comparison with etanercept.
[c] p =0.020 for ustekinumab 45 mg comparison with etanercept
[d] p=0.004 for ustekinumab 45 mg comparison with etanercept.
[e] p=0.303 for ustekinumab 45 mg comparison with etanercept.
[f] p=0.001 for ustekinumab 90 mg comparison with etanercept.
[g] Conventional systemic agents include psoralen plus ultraviolet A, MTX, and cyclosporine. Unsuitable conventional systemic agents are defined as those to which patients had had an inadequate response, were intolerant, or had a contraindication.

Clinical Efficacy – Pediatric plaque psoriasis

Adolescent patients (12 to 17 years of age)

The efficacy of Ustekinumab (Stelara®) was studied in 110 pediatric patients 12 to 17 years of age, in a multicenter, Phase 3, randomized, double blind, placebo controlled study (CADMUS). Patients were randomized to receive either placebo (n=37), or the recommended dose of Ustekinumab (Stelara®) (n=36) (see ***Dosage and Method of Administration***) or half the recommended dose of Ustekinumab (Stelara®) (n=37) by subcutaneous injection at Weeks 0 and 4 followed by every 12 week (q12w) dosing. At Week 12, placebo treated patients crossed over to receive Ustekinumab (Stelara®). Efficacy observed in patients treated with the recommended dose of Ustekinumab (Stelara®) is presented below.

The baseline disease characteristics of randomized subjects are summarized in Table 12. Patients with PASI ≥ 12, PGA ≥ 3 and BSA involvement of at least 10%, who were candidates for systemic or phototherapy, were eligible for the study. Approximately half of the patients had prior exposure to conventional systemic or biologic therapy.

Table 1: Baseline Disease Characteristics in pediatric patients 12 to 17 years of age: CADMUS

	Placebo	Ustekinumab (Stelara®)*
Patients randomized at Week 0	N= 37	N= 36
Median Age (years)	16.0	15.0
Males	20 (54.1%)	16 (44.4%)
Mean Weight (range; kg)	64.74 (43.8; 107.0)	62.00 (33.8; 109.5)
Median BMI (kg/m^2)	22.70	22.15
Median BSA	21.0	21.5
BSA ≥ 20%	20 (54.1%)	20 (55.6%)
Median PASI	19.6	16.8
Median CDLQI** (0-30)	10.0	9.0
Median PedsQL*** (0-100)	77.17	79.35
PGA of marked or severe	15 (40.5%)	12 (33.3%)
Psoriasis Disease Duration (years)	5.11	5.54
Prior topical therapy	34 (91.9%)	33 (91.7%)
Prior phototherapy	11 (29.7%)	14 (38.9%)
Prior conventional systemic therapy	16 (43.2%)	17 (47.2%)
Prior conventional systemic therapy or phototherapy	22 (59.5%)	22 (61.1%)
Prior biologic therapy	5 (13.5%)	3 (8.3%)
Prior conventional systemic or biologic therapy	18 (48.6%)	17 (47.2%)

* Data presented for the recommended dose of Ustekinumab (Stelara®)

** CDLQI: The CDLQI is a dermatology instrument to assess the effect of a skin problem on the health-related quality of life in the pediatric population, with higher scores indicating greater negative effect on health-related quality of life.

*** PedsQL: The PedsQL is a general health-related quality of life measure developed for use in children and adolescent populations.

The primary endpoint was the proportion of patients who achieved a PGA score of cleared (0) or minimal (1) at Week 12. Secondary endpoints included PASI 75, PASI 90, change from baseline in Children's Dermatology Life Quality Index (CDLQI), change from baseline in the total score of PedsQL (Pediatric Quality of Life Inventory) at Week 12. At Week 12, subjects treated with Ustekinumab (Stelara®) showed significantly greater improvement in their psoriasis and health related quality of life compared with placebo (Table 13).

Table 2: Summary of Primary and Secondary End-points at Week 12: CADMUS (Age 12-17)

	Placebo	Ustekinumab (Stelara®)*
	N (%)	N (%)
Patients randomized at Week 0	37	36
Number of patients who achieved a PGA score of cleared (0) or minimal (1)	2 (5.4%)	25 (69.4%)[a]
PGA of Cleared (0)	1 (2.7%)	17 (47.2%)[a]
PASI 75 responders	4 (10.8%)	29 (80.6%)[a]
PASI 90 responders	2 (5.4%)	22 (61.1%)[a]
PASI 100 responders	1 (2.7%)	14 (38.9%)[a]

Change from baseline in CDLQI score		
n	32	32
Mean (SD)	-1.5 (3.18)	-6.7 (5.63)
Median	0.0	-5.5
CDLQI of 0 or 1**	4 (13.3%)	17 (56.7%)[a]
Change from baseline in PedsQL Total Scale Score		
n	36	36
Mean (SD)	3.35 (10.04)	8.03 (10.44)[b]

* Data presented for the recommended dose of Ustekinumab (Stelara®)

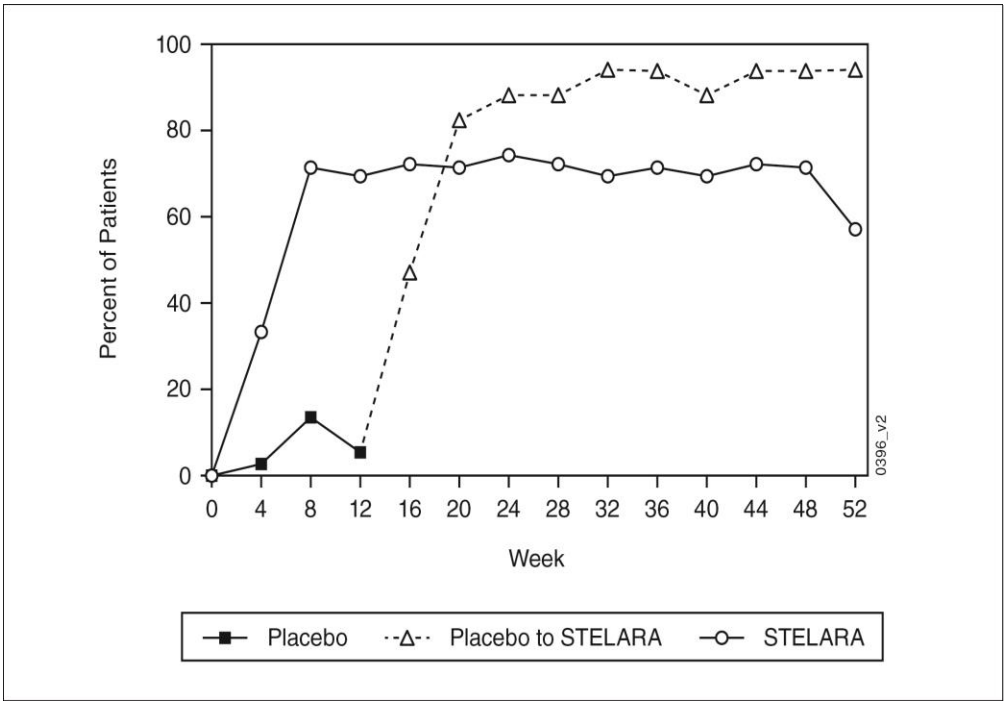
[a] p<0.001

[b] p=0.028

** CDLQI of 0 or 1 indicates no effect on child's quality of life.

All patients were followed for efficacy for up to 52 weeks following first administration of study agent. The proportion of patients with a PGA score of cleared (0) or minimal (1) and the proportion achieving PASI 75 showed separation between the Ustekinumab (Stelara®) treated group and placebo at the first post-baseline visit at Week 4 reaching a maximum at Week 8. Improvements in PGA, PASI, CDLQI and PedsQL were maintained through Week 52. The PGA scores of cleared (0) or minimal (1) over time through Week 52 are summarized in Figure 3 below.

Figure 1: Percent of patients achieving PGA score of cleared (0) or minimal (1) through Week 52 by visit*.



*Data presented for the recommended dose of Ustekinumab (Stelara®)

Pediatric patients (Children 6 to 11 years of age)

The efficacy of Ustekinumab (Stelara®) was studied in 44 pediatric patients 6 to 11 years of age with moderate to severe plaque psoriasis in an open label, single-arm, multicenter, Phase 3 study (CADMUS Jr.). Patients were treated with the recommended dose of Ustekinumab (Stelara®) (n=44) (see ***Dosage and Method of Administration***) by subcutaneous injection at Weeks 0 and 4 followed by every 12 week (q12w) dosing.

The baseline disease characteristics of enrolled patients are summarized in Table 14. Patients with PASI ≥ 12, PGA ≥ 3 and BSA involvement of at least 10%, who were candidates for systemic therapy or phototherapy, were eligible for the study. Approximately 23% of the patients had prior exposure to conventional systemic therapy or biologic therapy.

Table 3: Baseline Disease Characteristics in pediatric patients 6 to 11 years of age; CADMUS Jr.

	Ustekinumab (Stelara®)*
Patients enrolled at Week 0	N= 44
Median Age (years)	9.5
Males	17 (38.6%)
Mean Weight (range; kg)	38.4 (19; 99)
Median BMI (kg/m^2)	18.0
Median BSA	18.0
BSA ≥ 20%	19 (43.2%)
Median PASI	16.1
Median CDLQI** (0-30)	7.0
PGA of marked or severe	15 (34.1%)
Median Psoriasis Disease Duration (years)	2.9
Prior topical therapy	43 (97.7%)
Prior phototherapy	15 (34.1%)
Prior conventional systemic therapy	8 (18.2%)
Prior conventional systemic therapy or phototherapy	19 (43.2%)
Prior biologic therapy	2 (4.5%)
Prior conventional systemic or biologic therapy	10 (22.7%)

* Data presented for the recommended dose of Ustekinumab (Stelara®)

** CDLQI: The CDLQI is a dermatology instrument to assess the effect of a skin problem on the health-related quality of life in the pediatric population, with higher scores indicating greater negative effect on health-related quality of life.

The primary endpoint was the proportion of patients who achieved a PGA score of cleared (0) or minimal (1) at Week 12. Secondary endpoints included PASI 75, PASI 90, and change from baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 12. At Week 12, patients treated with Ustekinumab (Stelara®) showed clinically meaningful improvements in their psoriasis and health related quality of life (Table 15).

Table 15: Summary of Primary and Secondary End-points at Week 12 and 52: CADMUS Jr. (Age 6-11)		
	Ustekinumab (Stelara®) Week 12	Ustekinumab (Stelara®) Week 52
	N (%)	N (%)
Patients enrolled at Week 0	44	41
Number of patients who achieved a PGA score of cleared (0) or minimal (1)	34 (77.3%)	31 (75.6%)
PGA of cleared (0)	17 (38.6%)	23 (56.1%)
PASI 75 responders	37 (84.1%)	36 (87.8%)
PASI 90 responders	28 (63.6%)	29 (70.7%)
PASI 100 responders	15 (34.1%)	22 (53.7%)
Patients with a CDLQI >1 at baseline	N = 39	N = 36
CDLQI of 0 or 1*	24 (61.5%)	21 (58.3%)

* The CDLQI is a dermatology instrument to assess the effect of a skin problem on the health-related quality of life in the pediatric population. CDLQI of 0 or 1 indicates no effect on child's quality of life.

All patients were followed for efficacy for up to 52 weeks following first administration of study agent. Efficacy measured by PGA score of 0 or 1 was observed as early as the first post-baseline visit at Week 4 and increased through Week 16 and then remained relatively stable through Week 52. Improvements in PGA, PASI, and CDLQI were maintained through Week 52.

Clinical Efficacy – Psoriatic arthritis (PsA)

The safety and efficacy of Ustekinumab (Stelara®) was assessed in two multicenter, randomized, double-blind, placebo-controlled, Phase 3 studies, PSUMMIT I and PSUMMIT II, in patients with active psoriatic arthritis. Patients were randomized to receive treatment with either Ustekinumab (Stelara®) 45 mg, 90 mg, or placebo subcutaneous injections at Weeks 0 and 4 followed by every 12 week (q12w) dosing. The primary endpoint in these studies was the reduction in the signs and symptoms of psoriatic arthritis (PsA) as measured by the percentage of ACR 20 responders at Week 24. Secondary endpoints included change from baseline in Disability Index of the Health Assessment Questionnaire (HAQ-DI), PASI 75, ACR 50, ACR 70 and change from baseline in total radiographic scores of the hands and feet, at Week 24. Efficacy data were collected and analyzed through Week 52 for both studies and through Week 100 for PSUMMIT I. These studies included 927 (PSUMMIT I, n=615; PSUMMIT II, n=312) adult patients (≥18 years) who had active psoriatic arthritis (≥5 swollen joints and ≥5 tender joints, despite disease modifying antirheumatic (DMARD) and/or nonsteroidal anti-inflammatory (NSAID) therapy). Methotrexate use was allowed during the studies but was not mandatory. Approximately 50% of patients continued on stable doses of MTX (≤25 mg/week). In PSUMMIT I and PSUMMIT II, 80% and 86% of the patients, respectively, had been previously treated with DMARDs.

In PSUMMIT I patients, who had been previously treated with anti-TNFα therapy, prior to the first study dose, were excluded. In PSUMMIT II, the majority of patients (58%, n=180) had been previously treated with one or more anti-TNFα agent(s) for at least 8 weeks (14 weeks with infliximab) or had discontinued anti-TNFα for intolerance at any time. Among the patients who had been previously treated with an anti-TNFα agent, over 70% had discontinued their anti-TNFα treatment for lack of efficacy or intolerance.

Patients with each subtype of psoriatic arthritis were enrolled, including polyarticular arthritis with no evidence of rheumatoid nodules (39%, N=362), spondylitis with peripheral arthritis (28%, N=255), asymmetric peripheral arthritis (21%, N=193), distal interphalangeal (DIP) arthritis (12%, N=112) and arthritis mutilans (0.5%, N=5). Over 70% and 40% of the patients in both studies had enthesitis and dactylitis at baseline, respectively.

In both studies, a significantly greater proportion of patients achieved ACR 20 and ACR 50 responses at Week 24 in the Ustekinumab (Stelara®) 45 mg and 90 mg groups compared to placebo (see Table 16). In PSUMMIT I, a significantly greater proportion of patients and in PSUMMIT II a numerically greater proportion of patients (p=NS) achieved ACR 70 responses in the Ustekinumab (Stelara®) 45 mg and 90 mg groups compared to placebo (see Table 16).

In both studies, the proportion of patients achieving a modified PsA response criteria (PsARC) or a Disease Activity Index Score 28 using C-reactive protein (DAS28-CRP) response was significantly greater in the Ustekinumab (Stelara®) 45 mg and 90 mg groups compared to placebo. In PSUMMIT I the proportion of patients achieving DAS28-CRP remission was significantly greater in the Ustekinumab (Stelara®) 45 mg and 90 mg groups compared to placebo. In PSUMMIT II, the proportion of patients who achieved DAS28-CRP remission was significantly greater in the Ustekinumab (Stelara®) 90 mg group compared to placebo (see Table 16). DAS28-CRP and PsARC responses were maintained through Week 52 in both studies and through Week 100 in PSUMMIT I.

Table 16: Number of patients who achieved ACR 20, ACR 50, ACR 70, PsARC, DAS28-CRP response and DAS28-CRP remission at Week 24.

	PSUMMIT I			**PSUMMIT II**		
		Ustekinumab (Stelara®)			**Ustekinumab (Stelara®)**	
	Placebo (N=206)	**45 mg (N= 205)**	**90 mg (N= 204)**	**Placebo (N= 104)**	**45 mg (N= 103)**	**90 mg (N= 105)**
ACR 20	47 (23%)	87 (42%) [a]	101 (50%) [a]	21 (20%)	45 (44%)[a]	46 (44%) [a]
ACR 50	18 (9%)	51 (25%) [a]	57 (28%) [a]	7 (7%)	18 (17%) [b]	24 (23%) [a]
ACR 70	5 (2%)	25 (12%) [a]	29 (14%) [a]	3 (3%)	7 (7%) [c]	9 (9%) [c]
PsARC	77 (37%)	115 (56%) [a]	132 (65%) [a]	32 (31%)	57 (55%)[a]	54 (51%)[b]
DAS28-CRP[*]	71 (34%)	135 (66%) [a]	138 (68%) [a]	31 (30%)	56 (54%) [a]	56 (53%) [a]
DAS28 Remission**	17 (8%)	42 (20%) [a]	40 (20%) [a]	4 (4%)	11 (11%)[c]	16 (15%)[b]

[a] p<0.001

[b] p<0.05

[c] p= NS

[*] Combining tender joints (28 joints), swollen joints (28 joints), CRP, and the Patient Global Assessment of disease activity using CRP.

DAS28 responders include patients with moderate or good response.

**DAS28 remitters include patients with a DAS28 value of < 2.6 at a visit.

An ACR 20 response (Felson et al, 1995) was defined as:

1. ≥ 20% improvement in swollen joint count (66 joints) and tender joint count (68 joints); and
2. ≥ 20 % improvement in 3 of the following 5 assessments:

- Patient's assessment of pain [Visual Analog Scale (VAS)]
- Patient's global assessment of disease activity (VAS)
- Physician's global assessment of disease activity (VAS)
- Patient's assessment of physical function as measured by the HAQ-DI
- CRP

ACR 50 or ACR 70 are similarly defined.

The time course for ACR 20 response rates during the first 24 weeks in both studies for patients receiving Ustekinumab (Stelara®) or placebo are summarized in Figure 3. ACR 20 responses showed improvement at the first assessment (Week 4). ACR 20, 50 and 70 responses continued to improve or were maintained through Week 52 (see Table 17). In PSUMMIT I, ACR responses were maintained through Week 100.

Figure 4: Percent of patients achieving ACR 20 response through Week 24

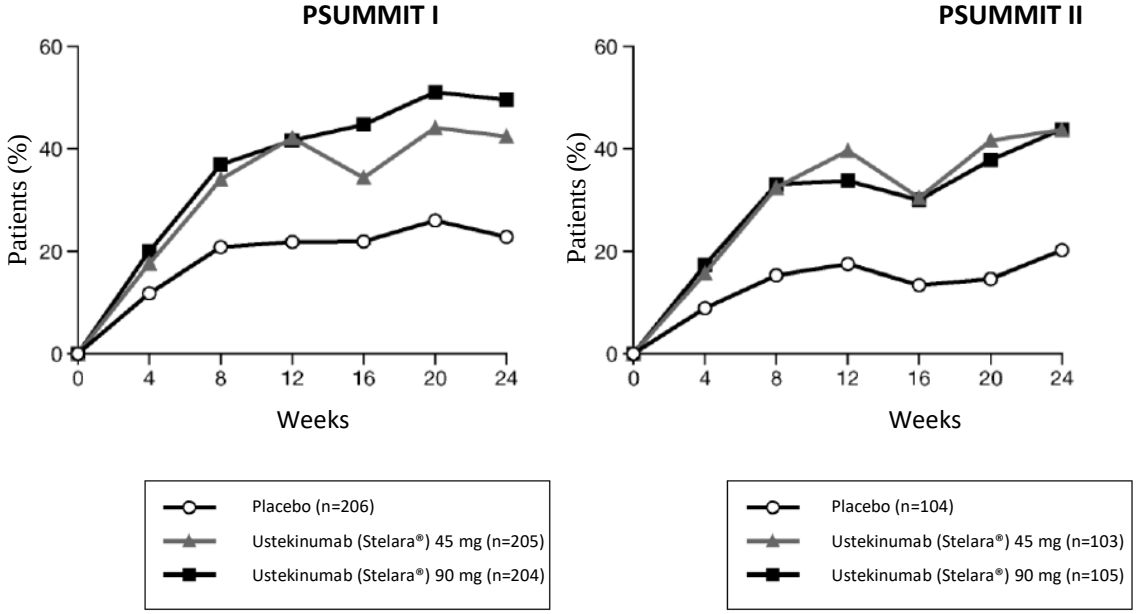


Table 47: Proportion of patients who achieved ACR 20, ACR 50, ACR 70 response at Week 52.

	PSUMMIT I		**PSUMMIT II**	
	Ustekinumab (Stelara®)		**Ustekinumab (Stelara®)**	
	45 mg	**90 mg**	**45 mg**	**90 mg**
N	194	189	94	95
ACR response				
ACR 20	55.7%	60.3%	46.8%	48.4%
ACR 50	31.4%	37.0%	27.7%	26.3%
ACR 70	18.0%	21.2%	12.8%	17.9%

In PSUMMIT I, of 205 subjects randomized to Ustekinumab (Stelara®) 45 mg, 153 continued the same dose and were available for evaluation at Week 52. Among those, ACR 20, 50 and 70 responses were achieved by 99 (64.7%), 57 (37.3%) and 34 (22.2%) subjects respectively. Of 204 subjects randomized to

Ustekinumab (Stelara®) 90 mg, 185 were available for evaluation at Week 52. Among those, ACR 20, 50 and 70 responses were achieved by 120 (64.9%), 74 (40%) and 41 (22.2%) subjects respectively.

In PSUMMIT I, of 205 subjects randomized to Ustekinumab (Stelara®) 45 mg, 138 continued the same dose and were available for evaluation at Week 100. Among those, ACR 20, 50 and 70 responses were achieved by 89 (64.5%), 63 (45.7%) and 41 (29.7%) subjects respectively. Of 204 subjects randomized to Ustekinumab (Stelara®) 90 mg, 166 were available for evaluation at Week 100. Among those, ACR 20, 50 and 70 responses were achieved by 116 (69.9%), 84 (50.6%) and 41 (24.7%) subjects respectively.

In PSUMMIT II, of 103 subjects randomized to Ustekinumab (Stelara®) 45 mg, 68 continued the same dose and were available for evaluation at Week 52. Among those, ACR 20, 50, and 70 responses were achieved by 41 (60.3%), 23 (33.8%) and 11 (16.2%) subjects respectively. Of 105 subjects randomized to Ustekinumab (Stelara®) 90 mg, 83 were available for evaluation at Week 52. Among those, ACR 20, 50 and 70 responses were achieved by 49 (59%), 26 (31.3%) and 17 (20.5%) subjects respectively.

Additionally, within each weight group (≤100 kg and >100 kg), ACR 20, ACR 50 and ACR 70 responses were consistently higher in the Ustekinumab (Stelara®) 45 and 90 mg groups than in the placebo group (see Table 18).

Table 18: Number of patients who achieved ACR 20, ACR 50 and ACR 70 responses by weight through Week 24

	PSUMMIT I			**PSUMMIT II**		
		Ustekinumab (Stelara®)			**Ustekinumab (Stelara®)**	
	Placebo (N=206)	**45 mg (N= 205)**	**90 mg (N= 204)**	**Placebo (N= 104)**	**45 mg (N= 103)**	**90 mg (N= 105)**
Patients randomized with weight ≤100 kg at baseline	154	153	154	74	74	73
ACR 20	39 (25%)	67 (44%)	78 (51%)	17 (23%)	32 (43%)	34 (47%)
ACR 50	14 (9%)	38 (25%)	48 (31%)	6 (8%)	15 (20%)	21 (29%)
ACR 70	5 (3%)	20 (13%)	26 (17%)	3 (4%)	6 (8%)	8 (11%)
Patients randomized with weight >100 kg at baseline	52	52	50	30	29	31
ACR 20	8 (15%)	20 (38%)	23 (46%)	4 (13%)	13 (45%)	12 (39%)
ACR 50	4 (8%)	13 (25%)	9 (18%)	1 (3%)	3 (10%)	3 (10%)
ACR 70	0	5 (10%)	3 (6%)	0	1 (3%)	1 (3%)

Ustekinumab (Stelara®) treatment resulted in significantly greater improvement compared with placebo for each ACR component (see Table 19).

Table 19: Summary of percent improvement from baseline in ACR components at Week 24						
	PSUMMIT I			**PSUMMIT II**		
		Ustekinumab (Stelara®)			**Ustekinumab (Stelara®)**	
	Placebo (N=206)	**45 mg (N= 205)**	**90 mg (N= 204)**	**Placebo (N=104)**	**45 mg (N= 103)**	**90 mg (N= 105)**
Number of swollen joints[d]						
Median	21.54	58.82[a]	60.00[a]	0.00	52.94[b]	50.00[c]
Number of tender joints[e]						
Median	13.61	45.45[a]	51.51[a]	0.00	33.33[a]	35.00[c]
Patient's assessment of pain[f]						
Median	0.00	31.33[a]	42.58[a]	0.00	24.19[a]	24.29[a]
Patient global assessment[f]						
Median	4.11	32.84[a]	42.44[a]	0.00	21.25[a]	22.54[a]
Physician global assessment[f]						
Median	17.64	48.39[a]	55.91[a]	0.83	36.67[a]	36.11[a]
Disability index (HAQ-DI)[g]						
Median	0.00	22.22[a]	32.46[a]	0.00	12.50[a]	14.29[a]
CRP (mg/dL)[h]						
Median	0.00	38.56[a]	48.30[a]	0.00	25.61[c]	33.69[a]

[a] p<0.001
[b] p<0.05
[c] p<0.01
[d] Number of swollen joints counted (0-66)
[e] Number of tender joints counted (0-68)
[f] Visual analogue scale; 0= best, 10=worst.
[g] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.
[h] CRP: (Normal Range 0.0-1.0 mg/dL)

Methotrexate Use

The proportion of patients achieving ACR responses were consistently greater in patients treated with Ustekinumab (Stelara®) than those treated with placebo regardless of concomitant MTX use (see Table 20). Responses observed in the Ustekinumab (Stelara®) groups were similar in patients receiving or not receiving concomitant MTX. ACR responses were maintained through Week 52 in PSUMMIT I and II and through Week 100 in PSUMMIT I.

Table 20: Summary of patients achieving ACR 20, ACR 50 and ACR 70 responses through Week 24 by methotrexate usage						
PSUMMIT I						
	Receiving MTX at baseline			*Not receiving MTX at baseline*		
		Ustekinumab (Stelara®)			**Ustekinumab (Stelara®)**	
	Placebo (N=206)	**45 mg (N= 205)**	**90 mg (N= 204)**	**Placebo (N=206)**	**45 mg (N= 205)**	**90 mg (N= 204)**
Patients randomized	96	99	101	110	106	103

ACR 20	25 (26%)	43 (43%)	46 (46%)	22 (20%)	44 (42%)	55 (53%)
ACR 50	8 (8%)	23 (23%)	27 (27%)	10 (9%)	28 (26%)	30 (29%)
ACR 70	2 (2%)	11 (11%)	13 (13%)	3 (3%)	14 (13%)	16 (16%)
PSUMMIT II						
	Receiving MTX at baseline			*Not receiving MTX at baseline*		
		Ustekinumab (Stelara®)			**Ustekinumab (Stelara®)**	
	Placebo (N=104)	**45 mg (N= 103)**	**90 mg (N= 105)**	**Placebo (N=104)**	**45 mg (N= 103)**	**90 mg (N= 105)**
Patients randomized	49	54	52	55	49	53
ACR 20	14 (29%)	27 (50%)	21 (40%)	7 (13%)	18 (37%)	25 (47%)
ACR 50	4 (8%)	10 (19%)	12 (23%)	3 (5%)	8 (16%)	12 (23%)
ACR 70	2 (4%)	4 (7%)	3 (6%)	1 (2%)	3 (6%)	6 (11%)

Prior Anti-TNFα therapy

PSUMMIT II evaluated 180 patients who were previously treated with one or more anti-TNFα agents for at least 8 weeks (14 weeks with infliximab), or had documented intolerance of anti-TNFα therapy at any time in the past.

Among patients previously treated with anti-TNFα agents, a significantly greater proportion of Ustekinumab (Stelara®)-treated patients achieved an ACR 20 response at Week 24 compared to placebo (see Table 21). ACR 20, 50, and 70 responses were generally maintained through Week 52.

Table 21: Number of patients previously treated with anti-TNFα agent(s) who achieved ACR 20, ACR 50 and ACR 70 responses through Week 24

PSUMMIT II		**Ustekinumab (Stelara®)**	
	Placebo (N= 104)	**45 mg (N= 103)**	**90 mg (N= 105)**
Patients randomized	62	60	58
ACR 20	9 (15%)	22 (37%)[a]	20 (34%)[b]
ACR 50	4 (6%)	9 (15%)[c]	9 (16%)[c]
ACR 70	1 (2%)	3 (5%)[c]	3 (5%)[c]

[a] p<0.01
[b] p<0.05
[c] p=NS

Enthesitis and Dactylitis

For patients with enthesitis and/or dactylitis at baseline, in PSUMMIT I, a significant improvement in enthesitis and dactylitis score was observed in the Ustekinumab (Stelara®) 45 mg and 90 mg groups compared to placebo. In PSUMMIT II, a significant improvement in enthesitis score and numerical improvement in dactylitis score were observed in the 90 mg group (p=NS) compared with the placebo group (see Table 22). In both studies, improvement in enthesitis score and dactylitis score were maintained at Week 52. In PSUMMIT I, the improvement in enthesitis score and dactylitis score was maintained through Week 100.

Table 22: Summary of percent change in enthesitis and dactylitis scores at Week 24						
	PSUMMIT I			**PSUMMIT II**		
		Ustekinumab (Stelara®)			**Ustekinumab (Stelara®)**	
	Placebo (N=206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N= 104)**	**45 mg (N= 103)**	**90 mg (N= 105)**
Enthesitis score [d]						
Patients randomized with enthesitis at baseline	145	142	154	73	72	76
N	137	140	148	68	70	70
Median	0.00	-42.86 [a]	-50.00 [b]	0.00	-33.33 [c]	-48.33[a]
Dactylitis score [e]						
Patients randomized with dactylitis at baseline	96	101	99	38	48	41
N	92	99	95	33	46	38
Median	0.00	-75.00 [b]	-70.83 [b]	0.00	0.00 [c]	-64.58 [c]

[a] p<0.01
[b] p<0.001
[c] p=NS
[d] Enthesitis was assessed based on the Maastricht Ankylosing Spondylitis Enthesis Score (MASES) index modified for PSA (an instrument that counts 15 body sites).
[e] Dactylitis was assessed in both hands and feet using a scoring system from 0 to 60.

A higher proportion of patients treated with Ustekinumab (Stelara®), that have spondylitis with peripheral arthritis as their primary presentation, demonstrated Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 and 70 percent improvement in BASDAI scores at Week 24 compared with placebo (see Table 23).

Table 23: Number of patients who achieved improvement from baseline in BASDAI at Week 24						
	PSUMMIT I			**PSUMMIT II**		
		Ustekinumab (Stelara®)			**Ustekinumab (Stelara®)**	
	Placebo (N= 206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N= 104)**	**45 mg (N=103)**	**90 mg (N=105)**
Patients randomized with spondylitis and peripheral joint involvement at baseline	70	52	64	22	26	22
N	61	51	60	18	25	21
BASDAI 20	16 (26%)	25 (49%)[a]	35 (58%)[b]	10 (56%)	15 (60%)[c]	11 (52%)[c]
BASDAI 50	8 (13%)	12 (24%)[c]	19 (32%)[a]	1 (6%)	7 (28%)[c]	8 (38%)[a]
BASDAI 70	0	7 (14%)[d]	9 (15%)[d]	0	3 (12%)*	5 (24%)*

[a] p≤0.05

[b] p<0.001
[c] p=NS
[d] p≤0.01
*p value not calculated

PASI Response

In PSUMMIT I and PSUMMIT II, the proportion of patients with psoriasis involvement of ≥3% BSA at baseline who achieved a ≥75% improvement in the PASI assessment at Week 24 was significantly greater in the Ustekinumab (Stelara®) 45 mg and 90 mg groups compared with the placebo group (see Table 24). In both studies the proportion of patients achieving the PASI 75 response was maintained through Week 52 (PSUMMIT I, Ustekinumab (Stelara®) 45 mg-70.1% and 90 mg- 68.1%; PSUMMIT II, Ustekinumab (Stelara®) 45 mg-56.6% and 90 mg- 64.4%). In PSUMMIT I, the PASI 75 response was maintained through Week 100.

The proportion of patients who achieved both a PASI 75 response and an ACR 20 response was evaluated for those patients with ≥3% BSA psoriasis skin involvement at baseline. A significantly higher proportion of patients achieved the combined response in the Ustekinumab (Stelara®) 45 mg and 90 mg groups compared with the placebo group at Week 24 (see Table 20). In both studies the proportion of patients achieving both a PASI 75 response and an ACR20 response was maintained through Week 52 (PSUMMIT I, Ustekinumab (Stelara®) 45 mg-44.8% and 90 mg-44.3%; PSUMMIT II, Ustekinumab (Stelara®) 45 mg-36.8% and 90 mg- 43.1%). In PSUMMIT I, the proportion of patients achieving the combined PASI 75 and ACR20 response was maintained through Week 100.

Table 24: Number of patients who achieved PASI 75, PASI 90 and PASI 100 responses as well as a combination of skin and joint responses at Week 24

	PSUMMIT I			**PSUMMIT II**		
		Ustekinumab (Stelara®) [a]			**Ustekinumab (Stelara®) [a]**	
	Placebo (N= 206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N= 104)**	**45 mg (N=103)**	**90 mg (N=105)**
Patients with ≥3% BSA psoriasis skin involvement at baseline	146	145	149	80	80	81
PASI 75	16 (11%)	83 (57%)	93 (62%)	4 (5%)	41 (51%)	45 (56%)
PASI 90	4 (3%)	60 (41%)	65 (44%)	3 (4%)	24 (30%)	36 (44%)
PASI 100	2 (1%)	29 (20%)	41 (28%)	1 (1%)	13 (16%)	17 (21%)
Combination of skin and joint responses						
PASI 75 and ACR 20	8 (5%)	40 (28%)	62 (42%)	2 (3%)	24 (30%)	31 (38%)

[a] p<0.001 for 45 mg or 90 mg comparison with placebo.

Additionally, within each weight group (≤100 kg and >100 kg), PASI 75, 90 and 100 responses were consistently higher in the Ustekinumab (Stelara®) 45 and 90 mg groups than in the placebo group (see Table 25).

Table 25: Summary of patients who achieved PASI 75, PASI 90 and PASI 100 responses by weight through Week 24

	PSUMMIT I			PSUMMIT II		
		Ustekinumab (Stelara®)			Ustekinumab (Stelara®)	
	Placebo (N=206)	45 mg (N= 205)	90 mg (N= 204)	Placebo (N= 104)	45 mg (N= 103)	90 mg (N= 105)
Patients randomized with weight ≤100 kg at baseline*	105	105	111	54	58	57
PASI 75	14 (13%)	64 (61%)	73 (66%)	4 (7%)	31 (53%)	32 (56%)
PASI 90	4 (4%)	46 (44%)	48 (43%)	3 (6%)	20 (34%)	27 (47%)
PASI 100	2 (2%)	21 (20%)	30 (27%)	1 (2%)	11 (19%)	13 (23%)
Patients randomized with weight >100 kg at baseline*	41	40	38	26	22	24
PASI 75	2 (5%)	19 (48%)	20 (53%)	0	10 (45%)	13 (54%)
PASI 90	0	14 (35%)	17 (45%)	0	4 (18%)	9 (38%)
PASI 100	0	8 (20%)	11 (29%)	0	2 (9%)	4 (17%)

* Patients randomized with ≥ 3% BSA psoriasis skin involvement at baseline

Methotrexate Use

In both studies, the proportion of patients who achieved a PASI 75 response at Week 24 was consistently higher in Ustekinumab (Stelara®) 45 mg and 90 mg groups compared with placebo regardless of concomitant MTX use. PASI 75 responses were maintained through Week 52 in both PSUMMIT I and II. In PSUMMIT I, PASI 75 response was maintained at Week 100.

Prior Anti-TNFα Therapy

In PSUMMIT II, the proportion of patients who achieved a PASI 75 response at Week 24 was significantly greater in Ustekinumab (Stelara®) 45 mg and 90 mg groups compared with placebo in patients previously treated with an anti-TNFα agent.

Radiographic Response

Structural damage in both hands and feet was assessed by readers unaware of treatment group and order of visits, and expressed as change in total van der Heijde-Sharp score (vdH-S score), modified for PsA by addition of hand distal interphalangeal (DIP) joints, compared to baseline. A pre-specified integrated analysis combining data from 927 subjects in both PSUMMIT I & II was performed. At Week 24, based on this integrated analysis, the Ustekinumab (Stelara®) 45 mg or 90 mg treatment significantly inhibited progression of structural damage, when compared to placebo (see Table 26). Beyond Week 24, Ustekinumab (Stelara®) treatment continued to inhibit the progression of structural damage through Week 52. The mean change from Week 24 to 52 in total modified vdH-S score (0.18 and 0.26 in the Ustekinumab (Stelara®) 45 mg and 90 mg groups respectively) was less than the mean change from Week 0 to 24 (see Table 26). In PSUMMIT I, the effect of Ustekinumab (Stelara®) on inhibition of structural damage progression was maintained through Week 100. Among subjects treated with Ustekinumab (Stelara®) 45 mg and 90 mg with no radiographic progression from baseline to Week 52

(n=103, and 113, respectively), 81.5% and 88.8% continued to show no radiographic progression at Week 100.

Table 56: Summary of change from baseline in total modified vdH-S score at Week 24 (Integrated analysis of PSUMMIT I and PSUMMIT II)

		Ustekinumab (Stelara®)	
	Placebo	45 mg	90 mg
Total Modified vdH-S score at Baseline			
N	306	303	300
Mean ± SD	28.01 ± 55.771	30.40 ± 50.688	27.97 ± 42.137
Change from Baseline			
N	310	308	309
Mean ± SD	0.97 ± 3.852	0.40 ± 2.110[b]	0.39 ± 2.403[a]

[a] p value < 0.001 for the difference between Ustekinumab (Stelara®) and Placebo, Week 24 (integrated analysis)
[b] p value < 0.05

At Week 24, patients treated with Ustekinumab (Stelara®) demonstrated less progression of structural damage compared to placebo, irrespective of concomitant MTX use.

The effect of Ustekinumab (Stelara®) on progression of structural damage in patients with prior anti-TNFα experience has not been established although it has not been adequately studied.

Physical Function and Health-Related Quality of Life

In PSUMMIT I and PSUMMIT II, physical function and health-related quality of life were assessed using the Disability Index of the Health Assessment Questionnaire (HAQ-DI), Dermatology Life Quality Index (DLQI) and the SF-36 health survey.

Patients treated with Ustekinumab (Stelara®) showed significant improvement in physical function as assessed by the HAQ-DI at Week 24. The proportion of patients achieving a clinically meaningful ≥0.3 improvement in HAQ-DI score from baseline at Week 24 was also significantly greater in the Ustekinumab (Stelara®) groups when compared with placebo (see Table 27). Improvement was observed at the first assessment (Week 4), reached maximum at Week 12 and was maintained through Week 24. Improvement in HAQ-DI score from baseline was maintained in both studies at Week 52 and through Week 100 in PSUMMIT I.

In both studies, the improvement in HAQ-DI at Week 24 was consistently greater in the Ustekinumab (Stelara®) 45 mg and 90 mg groups compared with placebo regardless of concomitant MTX use.

In PSUMMIT II, the improvement in HAQ-DI at Week 24 was significantly greater in the Ustekinumab (Stelara®) 45 mg and 90 mg groups compared with placebo in patients previously treated with anti-TNFα agents.

Table 27: Improvement in physical function as measured by HAQ-DI at Week 24						
	PSUMMIT I			**PSUMMIT II**		
		Ustekinumab (Stelara®)			**Ustekinumab (Stelara®)**	
	Placebo (N= 206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N= 104)**	**45 mg (N=103)**	**90 mg (N=105)**
HAQ-DI Baseline Score						
N	204	205	204	104	103	104
Mean (SD)	1.24 (0.647)	1.22 (0.610)	1.22 (0.634)	1.25 (0.723)	1.34 (0.704)	1.29 (0.666)
Median	1.25	1.25	1.25	1.25	1.38	1.25
Improvement in HAQ-DI						
N	206	205	204	104	103	105
Mean (SD)	0.10 (0.390)	0.31 (0.521)	0.40 (0.514)	0.03 (0.380)	0.21 (0.461)	0.22 (0.436)
Median	0.00	0.25 [a]	0.25 [a]	0.00	0.13 [b]	0.25 [a]
HAQ-DI Responders*	58 (28%)	98 (48%)[a]	97 (48%)[a]	17 (16%)	35 (34%)[b]	40 (38%)[a]

[a] p<0.001

[b] p<0.01

*achieving a ≥0.3 improvement from baseline

In PSUMMIT I, of 205 subjects randomized to Ustekinumab (Stelara®) 45 mg, 153 continued the same dose and were available for evaluation at Week 52. Among those, the HAQ-DI response was achieved by 83 (54.2%) subjects. Of 204 subjects randomized to Ustekinumab (Stelara®) 90 mg, 185 were available for evaluation at Week 52. Among those, HAQ-DI response was achieved by 102 (55.1%) subjects.

In PSUMMIT II, of 103 subjects randomized to Ustekinumab (Stelara®) 45 mg, 68 continued the same dose and were available for evaluation at Week 52. Among those, the HAQ-DI response was achieved by 29 (42.6%) subjects. Of 105 subjects randomized to Ustekinumab (Stelara®) 90 mg, 83 were available for evaluation at Week 52. Among those, HAQ-DI response was achieved by 44 (53%) subjects.

The DLQI was assessed by comparing the change in DLQI scores from baseline for those patients with ≥3% BSA at baseline. In both studies at Week 24, there was a significant improvement from baseline in DLQI scores in both the Ustekinumab (Stelara®) 45 mg and 90 mg groups as compared with placebo (see Table 28) and the improvement was maintained at Week 52. In PSUMMIT I, the improvement from baseline in DLQI scores was maintained through Week 100.

In both PSUMMIT I and PSUMMIT II, at Week 24, the change from baseline in the SF-36 physical component summary (PCS) scores was significantly greater in the Ustekinumab (Stelara®) 45 mg and 90 mg groups compared with the placebo group. In both studies, the change from baseline in the SF-36 mental component summary (MCS) scores at Week 24 was greater in both Ustekinumab (Stelara®) groups compared with the placebo group (p<0.001 for PSUMMIT I - 90 mg group, p=NS for other groups) (see Table 28). The change from baseline in the SF-36 PCS and MCS scores was maintained at Week 52 in both studies, and at Week 100 in PSUMMIT I.

In PSUMMIT II, a significant change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores was observed at Week 24 in the Ustekinumab (Stelara®) 45 mg and 90 mg

groups compared with the placebo group (median improvement, all 3.0 vs 0.0; p<0.007). Similarly, the percentage of patients with clinically significant improvement in fatigue from baseline (4 points in FACIT-F) was significantly greater in the Ustekinumab (Stelara®) 45 mg (49% [p<0.001]) and 90 mg groups (49% [p<0.001]) compared with the placebo group (25.8%). The change from baseline in the FACIT-F scores was maintained at Week 52.

Table 28: Summary of change from baseline in DLQI and SF-36 and scores at Week 24

	PSUMMIT I			**PSUMMIT II**		
		Ustekinumab (Stelara®)			**Ustekinumab (Stelara®)**	
	Placebo (N= 206)	**45 mg (N=205)**	**90 mg (N=204)**	**Placebo (N= 104)**	**45 mg (N=103)**	**90 mg (N=105)**
DLQI						
Patients randomized with ≥ 3% BSA psoriasis skin involvement at baseline	146	145	149	80	80	81
Baseline						
N	145	145	149	80	80	81
Mean (SD)	11.68 (7.705)	11.02 (7.308)	10.54 (7.179)	11.93 (7.622)	12.09 (7.667)	11.98 (7.754)
Median	11.00	10.00	9.00	11.00	11.00	10.00
Change from baseline						
N	140	142	146	73	77	75
Mean (SD)	-1.40 (6.177)	-6.63 (6.776)	-7.54 (6.524)	-0.75 (5.666)	-6.95 (7.719)	-7.16 (6.748)
Median	-1.00	-6.00 [a]	-6.00 [a]	0.00	-6.00 [a]	-6.00 [a]
SF-36						
Physical component summary						
Baseline						
N	203	203	204	104	102	104
Mean (SD)	31.39 (8.785)	31.16 (8.511)	31.45 (8.152)	30.28 (9.361)	28.69 (8.501)	28.93 (8.480)
Median	30.40	29.80	29.70	29.35	27.95	28.15
Change from baseline						
N	196	200	197	97	99	97
Mean (SD)	1.4 (7.094)	4.89 (9.333)	6.22 (8.747)	1.09 (5.892)	4.29 (8.594)	4.67 (8.758)
Median	1.15	3.90 [a]	5.80 [a]	0.00	2.70 [c]	3.50 [a]
Mental component summary						

Baseline						
N	203	203	204	104	102	104
Mean (SD)	43.51 (10.848)	42.77 (10.908)	43.48 (11.608)	42.11 (12.507)	43.27 (12.911)	42.81 (11.953)
Median	43.90	42.00	41.65	41.80	43.70	41.40
Change from baseline						
N	196	200	197	97	99	97
Mean (SD)	1.53 (9.582)	3.35 (10.016)	4.79 (10.054)	0.63 (8.238)	3.01 (11.144)	3.52 (11.274)
Median	0.25	2.65[b]	4.40[a]	0.00	0.70[b]	2.20[b]

[a] p≤0.001
[b] p=NS
[c] p<0.05

Health Economics
Health economics data on time lost from work, employability, and daily productivity at work, school, or home were collected through questionnaires at baseline and Week 24. To assess productivity, patients were asked to indicate how much their disease affected their productivity at work, school or at home in the past 4 weeks, using a 10 cm Visual Analogue Scale (VAS) (not at all affected [0] to affected very much [10]).

The improvement in self-reported productivity was significantly greater in the Ustekinumab (Stelara®) 45 mg and 90 mg groups compared to placebo at Week 24. The improvement in self-reported productivity was maintained in both studies at Week 52 and through Week 100 in PSUMMIT I.

Clinical Efficacy – Crohn's Disease
The safety and efficacy of Ustekinumab (Stelara®) were evaluated in three randomized, double-blind, placebo-controlled clinical trials in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450). The clinical development program consisted of two 8-week IV induction studies (UNITI-1 and UNITI-2) followed by a 44-week subcutaneous randomized withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

Induction of Clinical Response and Remission
UNITI-1 and UNITI-2 studies included 1409 (UNITI-1, n=769; UNITI-2 n=640) patients. In both studies, patients were permitted to concomitantly receive oral 5-ASA compounds, immunomodulators, corticosteroids, and/or antibiotics. Patients were randomized to receive a single IV administration of either 130 mg Ustekinumab (Stelara®), or approximately 6 mg/kg Ustekinumab (Stelara®) designed as a tiered dose based on patient body weight (Table 33) or placebo at Week 0. The primary endpoint was clinical response (defined as a reduction in CDAI score of ≥100 points or CDAI score <150) at Week 6. Secondary endpoints included clinical remission at Week 8, clinical response at Week 8, 70-point response at Week 3, and 70-point response at Week 6. Efficacy data were collected and analyzed through Week 8 for both studies.

In UNITI-1, patients had failed or were intolerant to prior anti-TNFα therapy. At baseline, approximately 46% (n=340) patients were receiving corticosteroids (including budesonide) and 31.4% of patients were receiving immunomodulators. Approximately 48% had failed 1 prior anti-TNFα therapy and 52% had

failed 2 or 3 prior anti- TNFα therapies (40.8% and 10.4%, respectively). In this study, 29.1% patients had an inadequate initial response (primary non-responders), 69.4% responded but subsequently lost response (secondary non-responders), and 36.4% were intolerant to anti-TNFα therapies.

Patients in UNITI-2 had failed at least one conventional therapy (corticosteroids or immunomodulators) and were either anti-TNFα naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%). At baseline, approximately 40% patients were receiving corticosteroids (including budesonide) and 35% patients were receiving immunomodulators.

In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended IV induction dose. In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the group treated with Ustekinumab (Stelara®), compared to placebo (Table 29, Figure 5). Clinical response and remission were significant as early as Week 3 in Ustekinumab (Stelara®) treated patients and continued to improve through Week 8 (Figure 5).

Table 29: Induction of Clinical Response and Remission in UNITI-1* and UNITI-2**

	UNITI-1		**UNITI-2**	
	Placebo N=247	**Ustekinumab (Stelara®) N=249**	**Placebo N=209**	**Ustekinumab (Stelara®) N=209**
Clinical Remission, Week 8	18 (7.3%)	52 (20.9%)[a]	41 (19.6%)	84 (40.2%)[a]
Clinical Response (100 point), Week 6	53 (21.5%)	84 (33.7%)[b]	60 (28.7%)	116 (55.5%)[a]
Clinical Response (100 point), Week 8	50 (20.2%)	94 (37.8%)[a]	67 (32.1%)	121 (57.9%)[a]
70 Point Response, Week 3	67 (27.1%)	101 (40.6%)[b]	66 (31.6%)	106 (50.7%)[a]
70 Point Response, Week 6	75 (30.4%)	109 (43.8%)[b]	81 (38.8%)	135 (64.6%)[a]

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission

70 point response is defined as reduction in CDAI score by at least 70 points

* Anti-TNFα failures

** Conventional therapy failures

[a] $p < 0.001$

[b] $p < 0.01$

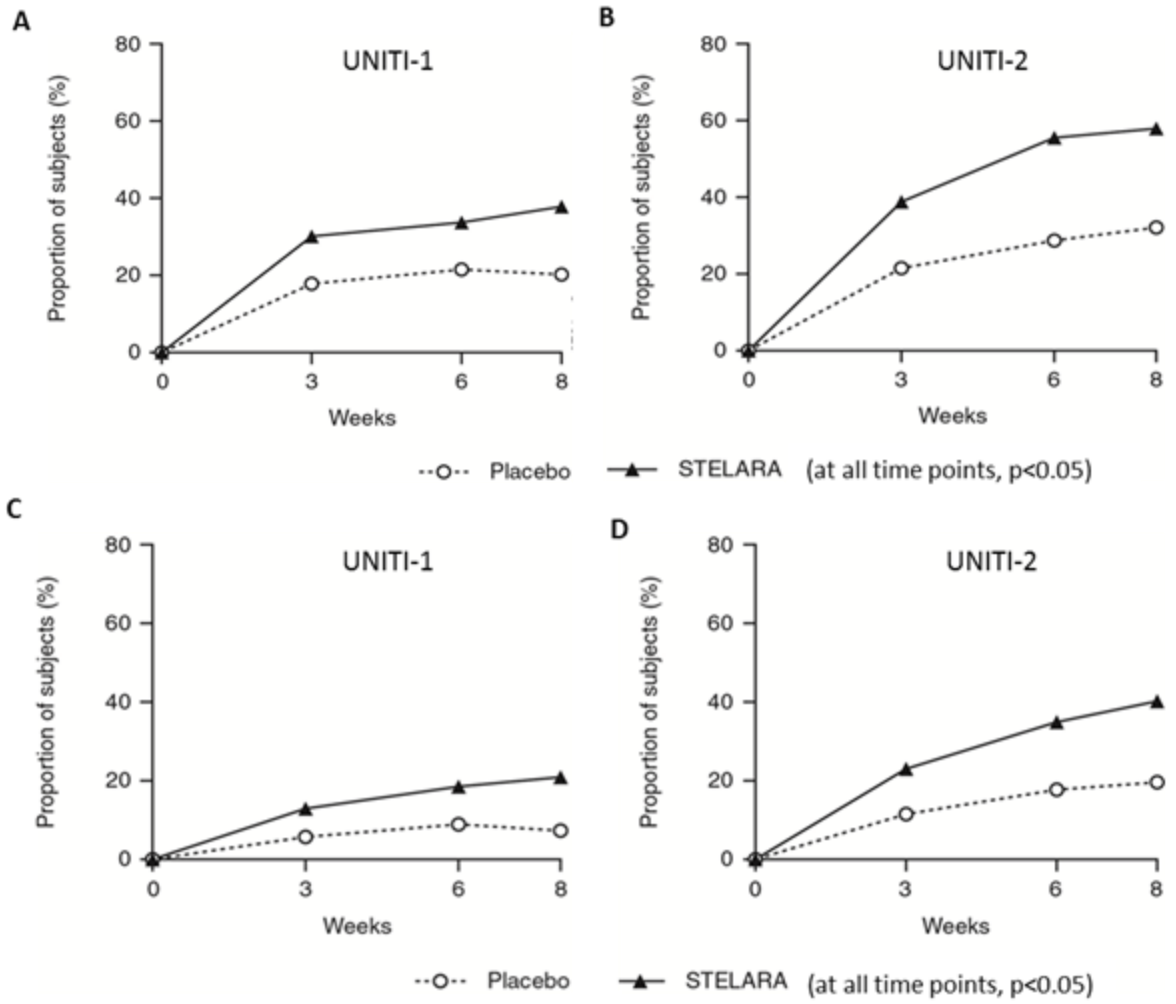


Figure 5: Proportion of Ustekinumab (Stelara®) treated patients in clinical response (A, B) and remission (C, D) through Week 8 in UNITI-1 and UNITI-2 studies

Maintenance of Response and Remission

The maintenance study (IM-UNITI) evaluated 388 patients who achieved clinical response (≥100 point reduction in CDAI score) at Week 8 of induction with Ustekinumab (Stelara®) in UNITI-1 or UNITI-2. Of those, approximately 60% of the patients entered the maintenance study in remission. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg Ustekinumab (Stelara®) every 8 weeks, 90 mg Ustekinumab (Stelara®) every 12 weeks or placebo for 44 weeks.

Concomitant doses of oral 5-ASA compounds, immunomodulators corticosteroids and antibiotics were permitted. Corticosteroids were tapered at the start of the maintenance trial. The primary endpoint was clinical remission (CDAI < 150) at Week 44. Secondary endpoints assessed at Week 44 included clinical response, clinical remission among Ustekinumab (Stelara®) treated patients in clinical remission after induction, corticosteroid-free remission, and clinical remission in the subset of patients who were refractory or intolerant to anti-TNFα treatment.

Significantly higher proportions of patients maintained clinical remission and response in the Ustekinumab (Stelara®) treated groups as compared to placebo at Week 44 (Table 30, Figure 6). A

higher proportion of Ustekinumab (Stelara®) treated patients compared to placebo achieved sustained clinical remission (clinical remission at Week 36, 40 and 44).

Table 30: Maintenance of Clinical Response and Remission in IM-UNITI (Week 44; 52 weeks from initiation of the induction dose)

	Placebo* **N=131†**	**90 mg Ustekinumab (Stelara®) every 8 weeks** **N=128†**	**90 mg Ustekinumab (Stelara®) every 12 weeks** **N=129†**
Clinical Remission	36%	53%[a]	49%[b]
Clinical Response	44%	59%[b]	58%[b]
Corticosteroid-Free Clinical Remission	30%	47%[a]	43%[c]
Sustained Clinical Remission‡	26%	46%[c]	40%[c]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who are Anti-TNFα refractory/intolerant	26% (16/61)	41% (23/56)	39% (22/57)
who failed conventional therapy but not anti-TNFα therapy	44% (31/70)	63% (45/72)[c]	57% (41/72)
who are Anti-TNFαnaïve	49% (25/51)	65% (34/52)[c]	57% (30/53)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

* The placebo group consisted of patients who were in response to Ustekinumab (Stelara®) and were randomized to receive placebo at the start of maintenance therapy.

† Patients who achieved a clinical response to Ustekinumab (Stelara®) at start of maintenance therapy

‡ Defined as clinical remission at Week 36, 40 and 44.

[a] $p < 0.01$

[b] $p < 0.05$

[c] nominally significant ($p<0.05$)

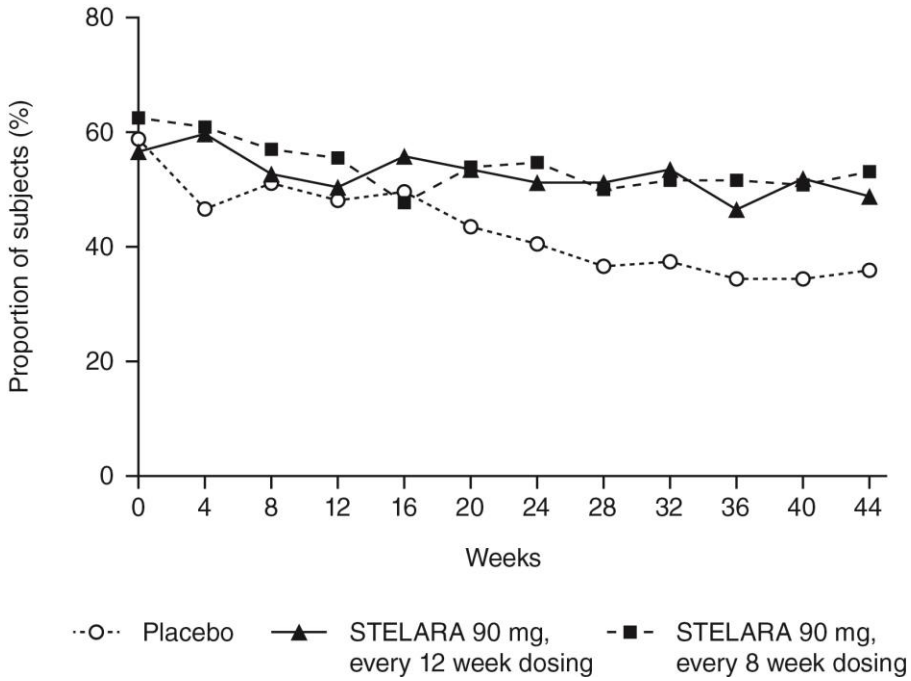


Figure 6: Proportion of patients in clinical remission at each visit through Week 44.

Delayed response
Patients who were not in clinical response to Ustekinumab (Stelara®) induction received a 90 mg subcutaneous injection of Ustekinumab (Stelara®) upon entry into the maintenance study. Eight weeks later, 50.5% of the patients achieved clinical response and continued to receive maintenance dosing every 8 weeks; among these patients with continued maintenance dosing, a majority achieved levels of response (68.1%) and remission (50.2%) similar to the patients who initially responded to Ustekinumab (Stelara®) induction.

Dosing in patients with a lower inflammatory burden
In patients with a lower inflammatory burden as reflected by CRP ≤ 10 mg/L at initiation of induction or initiation of maintenance therapy, the efficacy of the every 12 week dosing regimen was similar to that of the every 8 week dosing regimen.

Dosing frequency adjustment
In IM-UNITI, patients who did not maintain response to Ustekinumab (Stelara®) when treated every 12 weeks were allowed to increase the frequency of dosing and receive Ustekinumab (Stelara®) every 8 weeks. In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dosing frequency adjustment.

Resumption of treatment
Patients that responded to Ustekinumab (Stelara®) induction and who were randomized to the placebo group at the start of the maintenance study received 90 mg Ustekinumab (Stelara®) subcutaneously every 8 weeks at time of loss of response. Of these patients, 70.6% achieved clinical response and 39.2% achieved clinical remission 16 weeks after receiving the first subcutaneous dose of Ustekinumab (Stelara®).

Long-Term Maintenance
In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among patients who entered the study extension, clinical remission and response were generally maintained through week 92. Results were consistent between patients who failed TNF-therapies versus those who did not.

No new safety concerns were identified in this study extension with up to 5 years of treatment in patients with Crohn's Disease.

Corticosteroid Use in maintenance
In patients that were in clinical response to Ustekinumab (Stelara®) induction therapy, a greater proportion of patients in the Ustekinumab (Stelara®) treated group were in remission and corticosteroid-free compared to the placebo group after 44 weeks of maintenance treatment (Table 30). In addition, a higher proportion of patients were in clinical response and not receiving corticosteroids in the Ustekinumab (Stelara®) treated group compared to placebo.

Endoscopic Healing of the Mucosa
Endoscopic healing of the mucosa was evaluated in 252 patients with baseline endoscopic disease activity in a substudy. At Week 8, after a single IV induction dose, reduction in mucosal inflammation, as measured by the Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD), was greater in patients treated with Ustekinumab (Stelara®) (n=83) compared with patients treated with placebo (n=97) (-3.0 vs -0.7, p=0.009). Similar reductions in histologic inflammation were also observed.

Reduction in endoscopic and histologic inflammation was observed in patients treated with Ustekinumab (Stelara®) in maintenance. However, due to the small number of patients, the efficacy of Ustekinumab (Stelara®) in the maintenance of endoscopic healing could not be definitively established.

Fistula Response
In patients with draining fistulas at baseline (8.8%), a numerically greater proportion of Ustekinumab (Stelara®) treated patients achieved a fistula response (defined as ≥ 50% reduction from baseline of the induction study in the number of draining fistulas) compared with placebo over 44 weeks (p=NS). The proportion of patients in fistula response at Week 44 was 45.5% (5/11) for placebo group, 71.4% (5/7) for Ustekinumab (Stelara®) 90 mg every 12 week dosing group, and 87.5% (7/8) for Ustekinumab (Stelara®) 90 mg every 8 week dosing group.

Health-Related Quality of Life Measures
Improvement in general and disease specific health-related quality of life was assessed using the SF-36 and Inflammatory Bowel Disease Questionnaire (IBDQ) respectively.

SF-36
A higher proportion of patients treated with Ustekinumab (Stelara®) showed clinically meaningful improvements in SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, and these improvements were significantly greater at week 8 compared with the placebo group in UNITI-1 (MCS) and UNITI-2 (PCS, MCS and all subscores). These improvements in the PCS and MCS scores were maintained in Ustekinumab (Stelara®) treated patients in the IM-UNITI maintenance study through Week 44.

IBDQ

At Week 8 in UNITI-1 and UNITI-2, significant improvement from baseline in the inflammatory bowel disease questionnaire (IBDQ) total score and all subscales, was observed in the patients treated with Ustekinumab (Stelara®) compared to placebo. In both studies, a higher proportion of patients with clinically meaningful improvement in IBDQ total scores were observed in patients treated with Ustekinumab (Stelara®) compared to placebo. These improvements in the IBDQ total scores were maintained in Ustekinumab (Stelara®) treated patients in the IM-UNITI maintenance study through Week 44.

Long-term maintenance of health-related quality of life measures
Improvement in health-related quality of life as measured by IBDQ and SF-36 was generally maintained during the extension through week 92.

Clinical Efficacy – Ulcerative Colitis

The safety and efficacy of ustekinumab was assessed in two randomized, double-blind, placebo-controlled, multicenter studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥2 based on central review of the endoscopy). The clinical development program consisted of one intravenous induction study (referred to as UNIFI-induction) with treatment of up to 16 weeks followed by a 44-week subcutaneous randomized withdrawal maintenance study (referred to as UNIFI-maintenance) representing at least 52 weeks of therapy.

Efficacy results presented for UNIFI-induction and UNIFI-maintenance were based on central review of endoscopies.

UNIFI-induction included 961 patients. The primary endpoint for the induction study was the proportion of patients in clinical remission (defined as a Mayo score ≤2 points, with no individual subscore >1) at Week 8. Patients were randomized to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 33; Initial IV dosing of Ustekinumab (Stelara®)[a]), a fixed dose of 130 mg ustekinumab, or placebo at Week 0.

Concomitant use of oral corticosteroids, immunomodulators, and aminosalicylates were permitted and 90% of patients continued to receive at least one of these medications. Enrolled patients had to have failed conventional therapy (corticosteroids or immunomodulators) or at least one biologic (a TNFα antagonist and/or vedolizumab). 49% of patients had failed conventional therapy, but not a biologic (of which 94% where biological-naïve). 51% of patients had failed or were intolerant to a biologic. Approximately 50% of the patients had failed at least 1 prior anti-TNFα therapy (of which 48% were primary non-responders) and 17% had failed at least 1 anti-TNFα therapy and vedolizumab.

In UNIFI-induction a significantly greater proportion of patients were in clinical response and remission in the ustekinumab treated group compared to placebo (Table 31). As early as Week 2, the earliest scheduled study visit, and at each visit thereafter, a higher proportion of ustekinumab patients had no rectal bleeding or achieved normal stool frequency (defined as a stool frequency subscore of 0 or 1) as compared with placebo patients. Significant differences in partial Mayo score and symptomatic remission were observed between ustekinumab and placebo as early as Week 2. Efficacy was higher in the tiered dose group (6 mg/kg) compared to the 130 mg dose group in select endpoints, and tiered dosing is therefore the recommended intravenous induction dose.

Table 31: Summary of Key Efficacy Measures in UNIFI-Induction (Week 8)

Endpoint	**Placebo N = 319**		**Ustekinumab[†] N =322**	
	N	%	N	%
Clinical Remission[*]	20	6%	61	19% [a]
Biologic-naïve[-/]	*16/151*	*11%*	*37/147*	*25%*
Not biologic failure	*16/158*	*10%*	*39/156*	*25%*
Prior biological failure	*4/161*	*2%*	*22/166*	*13%*
Clinical Response[§]	100	31%	199	62%[a]
Biologic-naïve[-/]	*54/151*	*36%*	*98/147*	*67%*
Not biologic failure	*56/158*	*35%*	*104/156*	*67%*
Prior biological failure	*44/161*	*27%*	*95/166*	*57%*
Endoscopic Healing[€]	44	14%	87	27%[a]
Biologic-naïve[-/]	*32/151*	*21%*	*49/147*	*33%*
Not biologic failure	*33/158*	*21%*	*52/156*	*33%*
Prior biologic failure	*11/161*	*7%*	*35/166*	*21%*
Histo-Endoscopic Mucosal Healing[‡]	28/316	9%	58/315	18% [a]
Biologic-naïve[-/]	*21/148*	*14%*	*33/140*	*24%*
Not biologic failure	*22/155*	*14%*	*36/149*	*24%*
Prior biological failure	*6/161*	*4%*	*22/166*	*13%*
Symptomatic Remission[£]	72	23%	144	45%[b]
Combined Symptomatic Remission and Endoscopic Healing[+]	25	8%	67	21% [b]

[†] Infusion dose of ustekinumab using the weight-based dosage regimen specified in Table 29.

[-/]An additional 7 patients on placebo and 9 patients on ustekinumab (6mg/kg) had been exposed to, but had not failed, biologics

*Clinical remission is defined as an absolute stool number ≤ 3, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1.

[§] Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

[€] Endoscopic healing is defined as a Mayo endoscopic subscore of 0 or 1 determined by central review of the endoscopy.

[‡] Histo-endoscopic mucosal healing is defined as combined endoscopic healing (Mayo endoscopy subscore of 0 or 1) and histologic healing of the colon tissue (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue).

[£] Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.

[+] Combined symptomatic remission and endoscopic healing is defined as remission based on a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.

[a] $p < 0.001$

[b] Nominally significant ($p < 0.001$)

UNIFI-maintenance evaluated 523 patients who achieved clinical response with single IV administration of ustekinumab in UNIFI-induction. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks.

Significantly greater proportions of patients were in clinical remission at Week 44 and maintained clinical response through Week 44 in both ustekinumab treated groups compared to the placebo group (see Table 32).

Table 32: Summary of Key Efficacy Measures in UNIFI-Maintenance (Week 44; 52 weeks from initiation of the induction dose)

	Placebo* **N** = 175	**Ustekinumab 90 mg every 8 Weeks** **N** = 176	**Ustekinumab 90 mg every 12 Weeks** **N** = 172
Clinical Remission[**]	25%	43% [a]	40% [b]
Biologic-naïve[ɻ]	*33% (28/84)*	*48% (38/79)*	*49% (47/95)*
Not biologic failure	*32% (28/87)*	*48% (41/85)*	*50% (51/102)*
Prior biologic failure	*17% (15/88)*	*37% (34/91)*	*24% (17/70)*
Maintenance of Clinical Response through Week 44[§]	45%	71% [a]	68% [a]
Biologic-naïve[ɻ]	*52% (44/84)*	*77% (61/79)*	*77% (73/95)*
Not biologic failure	*51% (44/87)*	*78% (66/85)*	*76% (78/102)*
Prior biologic failure	*39% (34/88)*	*65% (59/91)*	*56% (39/70)*
Corticosteroids Free Clinical Remission[‡]	24%	41% [a]	39% [b]
Biologic-naïve[ɻ]	*33% (28/84)*	*47% (37/79)*	*48% (46/95)*
Not biologic failure	*32% (28/87)*	*47% (40/85)*	*49% (50/102)*
Prior biologic failure	*16% (14/88)*	*35% (32/91)*	*24% (17/70)*
Endoscopic Healing at Week 44[†]	29%	51% [a]	44% [b]
Biologic-naïve[ɻ]	*36% (30/84)*	*58% (46/79)*	*55% (52/95)*
Not biologic failure	*34% (30/87)*	*58% (49/85)*	*56% (57/102)*
Prior biologic failure	*23% (20/88)*	*45% (41/91)*	*26% (18/70)*
Maintenance of Clinical Remission through Week 44[£]	33%	61% [c]	62% [c]
Biologic-naïve[ɻ]	*36% (10/28)*	*76% (16/21)*	*66% (25/38)*
Not biologic failure	*36% (10/28)*	*71% (17/24)*	*68% (27/40)*

Prior biologic failure	*30% (6/20)*	*50% (10/20)*	*42% (5/12)*
Durable Partial Mayo Remission through week 44[‖]	35%	57% [c]	48% [c]
Symptomatic Remission at Week 44[£]	45%	68% [c]	62% [c]
Combined Symptomatic Remission and Endoscopic Healing at Week 44[€]	28%	48% [c]	41% [c]

* The placebo group consisted of patients who were in response to ustekinumab IV and were randomized to receive placebo at the start of maintenance therapy.
**Clinical remission is defined as an absolute stool number ≤ 3, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1.
[§] Clinical response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.
[┼] An additional 3 patients on placebo and 6 patients on Q8W, 7 patients on Q12W ustekinumab had been exposed to, but had not failed, biologics
[†] Endoscopic healing is defined as a Mayo endoscopic subscore of 0 or 1 determined by central review of the endoscopy
[‡] Corticosteroid-free clinical remission was defined as patients in clinical remission and not receiving corticosteroids at Week 44.
[£]Maintenance of clinical remission is defined as patients in clinical remission at maintenance baseline through Week 44 among patients in clinical remission at maintenance baseline.
[‖] Durable partial Mayo remission is defined as partial Mayo remission (i.e. a partial Mayo score of ≤2) at ≥80% of all visits prior to Week 44 and in partial Mayo remission at last visit (Week 44).
[£] Symptomatic remission is defined as a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0.
[€]Combined symptomatic remission and endoscopic healing is defined as a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1.
[a] p< 0.001
[b] p<0.05
[c] Nominally significant (p < 0.05)

The beneficial effect of ustekinumab on clinical response, mucosal healing and clinical remission was observed in induction and in maintenance both in patients who failed conventional therapy but not a biologic therapy, as well as in those who had failed at least one prior TNFα antagonist therapy, and/or vedolizumab including in patients with a primary non-response to TNFα antagonist therapy.

Delayed Responders to Ustekinumab Induction
Ustekinumab treated patients who were not in response at Week 8 of UNIFI-induction received an administration of 90 mg SC ustekinumab at Week 8 (36% of patients). Of those patients, 12% of patients who were initially randomized to the recommended induction dose achieved clinical remission and 58% achieved clinical response at Week 16. When combining the delayed responders with the initial responders, 80% of subjects randomized to the recommended induction dose in UNIFI-I achieved clinical response and 22% achieved clinical remission within 16 weeks after initiating treatment with ustekinumab.

Patients who were not in clinical response to ustekinumab induction at Week 8 of the UNIFI-induction study but were in response at Week 16 (157 patients) entered in the non-randomized portion of UNIFI-maintenance and continued to receive maintenance dosing every 8 weeks; among these patients, a majority (62%) maintained response and 31% achieved remission at Week 44.

Endoscopic Normalization

Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0 and was observed as early as Week 8 of UNIFI-induction. At Week 44 of UNIFI-maintenance, it was achieved in 24% and 29% of patients treated with ustekinumab every 12 or 8 weeks, respectively, as compared to 18% of patients in the placebo group.

Histologic & Histo-Endoscopic Mucosal Healing

Histologic healing (defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) was assessed at Week 8 of UNIFI-induction and Week 44 of UNIFI-maintenance. At Week 8, after a single intravenous induction dose, significantly greater proportions of patients in the recommended dose group achieved histologic healing (36%) compared with patients in the placebo group (22%). At Week 44 maintenance of this effect was maintained with significantly more patients in histologic healing in the every 12 week (54%) and every 8 week (59%) ustekinumab groups as compared to placebo (33%).

A combined endpoint of histo-endoscopic mucosal healing defined as subjects having both mucosal healing and histologic healing was evaluated at week 8 of UNIFI-induction and Week 44 of UNIFI-maintenance. Patients receiving ustekinumab at the recommended dose showed significant improvements on the histo-endoscopic mucosal healing endpoint at Week 8 in the ustekinumab group (18%) as compared to the placebo group (9%). At Week 44, maintenance of this effect was observed with significantly more patients in histo-endoscopic mucosal healing in the every 12 week (39%) and every 8 week (46%) ustekinumab groups as compared to placebo (24%).

Health-related quality of life

Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ), SF-36 and EuroQoL-5D (EQ-5D) questionnaires. At Week 8 of UNIFI-induction, patients receiving ustekinumab showed significantly greater and clinically meaningful improvements on IBDQ total score, EQ-5D and EQ-5D VAS, and SF-36 Mental Component Summary Score and SF-36 Physical Component Summary Score when compared to placebo. These improvements were maintained in ustekinumab-treated patients in UNIFI-maintenance through Week 44.

Patients receiving ustekinumab experienced significantly more improvements in work productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI-GH questionnaire than patients receiving placebo.

Hospitalizations and Ulcerative Colitis related surgeries

Through Week 8 of UNIFI-induction, the proportions of subjects with ulcerative colitis disease related hospitalizations were significantly lower for subjects in the ustekinumab recommended dose group (1.6%, 5/322) compared with subjects in the placebo group (4.4%, 14/319) and no subjects underwent ulcerative colitis disease related surgeries in subjects receiving ustekinumab at the recommended induction dose compared to 0.6% (2/319) subjects in the placebo group.

Through Week 44 of UNIFI-maintenance, a significantly lower number of ulcerative colitis disease related hospitalizations was observed in subjects in the combined ustekinumab group (2.0%, 7/348) as compared with subjects in the placebo group (5.7%, 10/175). A numerically lower number of subjects in the ustekinumab group (0.6%, 2/348) underwent ulcerative colitis disease related surgeries compared with subjects in the placebo group (1.7%, 3/175) through Week 44.

Hospitalizations and ulcerative colitis related surgeries
Through Week 8 in Study UC-1, the proportions of patients with ulcerative colitis disease related hospitalizations or surgeries were lower for patients in the Ustekinumab (Stelara®) IV 6 mg/kg group, 1.6% (5/322) compared with patients in the placebo group 4.4% (14/319).

Pharmacokinetic Properties
Absorption
The median time to reach the maximum serum concentration (t_{max}) was 8.5 days after a single 90 mg subcutaneous administration in healthy subjects. The median t_{max} values of ustekinumab following a single subcutaneous administration of either 45 mg or 90 mg in patients with psoriasis were comparable to that observed in healthy subjects.

The absolute bioavailability of ustekinumab following a single subcutaneous administration was estimated to be 57.2% in patients with psoriasis. Following the recommended intravenous induction dose, median peak serum ustekinumab concentration was 126.1 mcg/mL in patients with Crohn's disease, and 127.0 mcg/mL in patients with ulcerative colitis.

Distribution
Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg. In a population pharmacokinetic analysis of ustekinumab, the volume of distribution at steady-state was 4.62 L in patients with Crohn's disease and 4.44 L in patients with ulcerative colitis.

Metabolism
The exact metabolic pathway for ustekinumab is unknown.

Elimination
Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg.

Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with ulcerative colitis, Crohn's disease, psoriasis and/or psoriatic arthritis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies. In a population pharmacokinetic analysis of ustekinumab, the clearance was 0.19 L/day while the half-life was approximately 19 days in patients with Crohn's disease and ulcerative colitis.

Dose Linearity
The systemic exposure of ustekinumab (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg or following a single subcutaneous administration at doses ranging from approximately 24 mg to 240 mg in patients with psoriasis.

Single Dose vs. Multiple Doses
Serum concentration-time profiles of ustekinumab were generally predictable after single or multiple subcutaneous dose administrations. In patients with psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28 after initial subcutaneous doses at Weeks 0 and 4, followed by doses every 12 weeks. The median steady-state trough concentration ranged from 0.21 mcg/mL to 0.26 mcg/mL (45 mg) and from 0.47 mcg/mL to 0.49 mcg/mL (90 mg).

Following the recommended IV induction dose, median peak serum ustekinumab concentration was 126.1 mcg/mL in patients with Crohn's disease and 127.0 mcg/mL in patients with ulcerative colitis. Starting at Week 8, subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 or 12 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 8 or 12 weeks.

Following subcutaneous maintenance dosing of 90 mg ustekinumab every 8 weeks, median steady-state trough concentrations ranged from 1.97 mcg/mL to 2.24 mcg/mL in patients with Crohn's disease and 2.69 mcg/mL to 3.09 mcg/mL in patients with ulcerative colitis. Following subcutaneous maintenance dosing of 90 mg ustekinumab every 12 weeks, median steady state trough concentrations ranged from 0.61 mcg/mL to 0.76 mcg/mL in patients with Crohn's disease and 0.92 mcg/mL to 1.19 mcg/mL in patients with ulcerative colitis. The steady-state trough ustekinumab levels resulting from 90 mg ustekinumab every 8 weeks were associated with higher clinical remission rates as compared to the steady state trough levels following 90 mg every 12 weeks.

Dosing Frequency Adjustment

In patients with Crohn's disease, based on observed data and population PK analyses, randomized subjects who lost response to treatment had lower serum ustekinumab concentrations over time compared with subjects who did not lose response. In Crohn's disease, dose adjustment from 90 mg every 12 weeks to 90 mg every 8 weeks was associated with an increase in trough serum ustekinumab concentrations and an accompanying increase in efficacy. In ulcerative colitis, population PK model based simulations demonstrated that adjusting dosing from 90 mg every 12 weeks to every 8 weeks would be expected to result in a 3-fold increase in steady-state trough ustekinumab concentrations. Additionally on the basis of clinical trial data in patients with ulcerative colitis, a positive exposure-response relationship was established between trough concentrations and clinical response, clinical remission, and mucosal healing.

Impact of Weight on Pharmacokinetics

Serum ustekinumab concentrations were affected by weight in patients with psoriasis and/or psoriatic arthritis. Within each dose (45 mg or 90 mg), patients of higher weight (> 100 kg) had lower median serum ustekinumab concentrations compared with those in patients of lower weight (≤ 100 kg). However, across doses, the median trough serum concentrations of ustekinumab in patients with higher weight (> 100 kg) in the 90 mg group were comparable to those in patients with lower weight (≤ 100 kg) in the 45 mg group.

Population Pharmacokinetic Analysis

In a population pharmacokinetic analysis using data from patients with psoriasis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 L/d and 15.7 L, respectively, and the $t_{1/2}$ was approximately 3 weeks in patients with psoriasis. The CL/F of ustekinumab was not impacted by sex, age, or race. The CL/F was impacted by body weight, with a trend toward higher CL/F in patients with higher body weight. The median CL/F in patients with weight > 100 kg was approximately 55% higher compared with patients with weight ≤ 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared with patients with weight ≤ 100 kg. Similar results were obtained from a confirmatory population pharmacokinetic analysis using data from patients with psoriatic arthritis.

In the population pharmacokinetic analysis using data from patients with psoriasis, the effect of comorbidities (past and current history of diabetes, hypertension, and hyperlipidemia) on pharmacokinetics of ustekinumab was evaluated. The pharmacokinetics of ustekinumab were impacted by the comorbidity of diabetes, with a trend towards higher CL/F in patients with diabetes. The mean CL/F in patients with diabetes was approximately 29% higher compared with patients without diabetes.

Population pharmacokinetic analysis showed that there was a trend towards a higher clearance of ustekinumab in patients with positive immune response.

No specific drug-drug interaction studies have been conducted in healthy subjects or patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis.

In the population pharmacokinetic analyses, the effect of the most frequently used concomitant medications in patients with psoriasis (including paracetamol/acetaminophen, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, naproxen, levothyroxine, hydrochlorothiazide, and influenza vaccine) on pharmacokinetics of ustekinumab was explored and none of the concomitant medications exerted significant impact. The pharmacokinetics of ustekinumab was not impacted by the prior use of MTX, cyclosporine, or other biological therapeutics for the treatment of psoriasis. The pharmacokinetics of ustekinumab was not impacted by concomitant use of NSAIDs or prior exposure to anti-TNFα agents in patients with psoriatic arthritis; or by the use of MTX, oral corticosteroids, 6-MP, AZA in patients with psoriatic arthritis or Crohn's disease, or by prior exposure to biologics (i.e. anti-TNFα agents and/or vedolizumab) in patients with ulcerative colitis.

The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4 (see ***Interactions with Other Medicinal Products and Other Forms of Interaction***).

Special Populations

Pediatrics (6 to 17 years of age)

The pharmacokinetics of ustekinumab in pediatric psoriasis patients, 6 to 17 years of age, treated with the recommended dose was generally comparable to that in the adult psoriasis population. No pharmacokinetic data are available in pediatric patients with Crohn's disease or ulcerative colitis.

Elderly (65 years of age and older)

No specific studies have been conducted in elderly patients. The population pharmacokinetic analysis indicated there were no apparent changes in CL/F and V/F estimates in patients ≥65 years.

Renal impairment

No pharmacokinetic data are available in patients with renal insufficiency.

Hepatic impairment

No pharmacokinetic data are available in patients with impaired hepatic function.

Other populations

The pharmacokinetics of ustekinumab were generally comparable between Asian and non-Asian patients with psoriasis, Crohn's disease, or ulcerative colitis.

The pharmacokinetics of ustekinumab were not impacted by the use of tobacco or alcohol.

NON-CLINICAL INFORMATION

In repeated-dose toxicity studies in juvenile cynomolgus monkeys, ustekinumab was well-tolerated following IV doses up to 45 mg/kg/week for up to 1 month and following twice-weekly SC doses up to 45 mg/kg for 6 months. There were no ustekinumab-related findings in the immunotoxicity and cardiovascular safety pharmacology evaluations. In histopathology evaluations there were no preneoplastic changes observed.

There were no adverse effects in monkeys at exposures that were 179-fold higher than the peak serum concentration in humans following 90 mg weekly subcutaneous injection and 29-fold higher than the peak serum concentration in humans following 6 mg/kg IV administration.

Carcinogenicity and Mutagenicity

Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.

Reproductive Toxicology

Three developmental toxicity studies were conducted in cynomolgus monkeys. No ustekinumab-related maternal toxicity, abortions, still-births, embryotoxicity, developmental delays, malformations or birth defects were observed at doses up to 45 mg/kg following weekly or twice weekly administration of ustekinumab via the IV or SC routes, respectively. In neonates born from pregnant monkeys treated with ustekinumab no adverse effects on growth or functional development were observed and no deficits were observed in immunotoxicity evaluations. In a male fertility study in cynomolgus monkeys no ustekinumab-related effects on mating behavior, sperm parameters, or serum concentrations of male hormones were observed following twice weekly subcutaneous administration of ustekinumab at doses up to 45 mg/kg.

A female fertility toxicity study was conducted in mice using an analogous antibody that binds to and inhibits IL-12 and IL-23 activity in mice. Twice weekly subcutaneous administration of the anti-mouse IL-12/23 antibody was well tolerated at doses up to 50 mg/kg and no adverse effects on female fertility parameters were observed.

THERAPEUTIC INDICATIONS

Plaque Psoriasis:

Adults

Ustekinumab (Stelara®) is indicated for:

- Treatment of psoriasis
- Improving health related quality of life

in adults with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Pediatric population

Ustekinumab (Stelara®) is indicated for:

- Treatment of psoriasis
- Improving health related quality of life

in pediatric patients (children and adolescents) age 6 years and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

Psoriatic Arthritis (PsA):
Ustekinumab (Stelara®), alone or in combination with methotrexate (MTX), is indicated for:

- Reducing signs and symptoms
- Improving physical function
- Inhibiting the progression of structural damage
- Improving enthesitis
- Improving psoriasis
- Improving health-related quality of life

in adults with active psoriatic arthritis

Crohn's Disease
Ustekinumab (Stelara®)

- Inducing and maintaining clinical response
- Inducing and maintaining clinical remission
- Eliminating corticosteroid use
- Inducing endoscopic healing
- Improving health-related quality of life

  in adults with moderately to severely active Crohn's disease who:
  - Have failed or were intolerant to immunomodulators or corticosteroids or
  - Were corticosteroid dependent or
  - Have failed or were intolerant to one or more anti-TNF treatment

Ulcerative Colitis
Ustekinumab (Stelara®) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

DOSAGE AND METHOD OF ADMINISTRATION
Dosage – (Adults)

Plaque Psoriasis
For the treatment of plaque psoriasis, Ustekinumab (Stelara®) is administered by subcutaneous injection. The recommended dose of Ustekinumab (Stelara®) is 45 mg administered at Weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight greater than 100 kg.

Dose Adjustment
For patients who inadequately respond to 45 mg every 12 weeks, consideration may be given to treating with 90 mg every 12 weeks. For patients who inadequately respond to dosing every 12 weeks, a 90 mg dose every 8 weeks may be considered.

Re-treatment
Re-treatment with a dosing regimen of Weeks 0 and 4 after interruption of therapy has been shown to be safe and effective.

Psoriatic Arthritis

For the treatment of psoriatic arthritis, Ustekinumab (Stelara®) is administered by subcutaneous injection. The recommended dose of Ustekinumab (Stelara®) is 45 mg administered at Weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight greater than 100 kg.

Crohn's Disease and Ulcerative Colitis

In patients with Crohn's disease, the recommended treatment regimen is a single intravenous (IV) tiered dose of Ustekinumab (Stelara®) based on body weight (Table 33), followed by 90 mg subcutaneous dosing 8 weeks later, then every 8 weeks thereafter (see ***Instructions for Use, Handling and Disposal***).

Table 33: Initial IV dosing of Ustekinumab (Stelara®)[a]

Body Weight of Patient at the time of dosing	Dose	Number of 130 mg Ustekinumab (Stelara®) Vials
≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

[a] Recommended dose (approximately 6 mg/kg)

For some patients, a single IV dose based on body weight (Table 33) followed by 90 mg subcutaneous dosing 8 weeks later, then every 12 weeks thereafter may be acceptable. Patients who inadequately respond to 90 mg subcutaneous dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see ***Clinical Studies***).

Immunomodulators and/or corticosteroids may be continued during treatment with Ustekinumab (Stelara®). In patients who have responded to treatment with Ustekinumab (Stelara®) corticosteroids may be reduced or discontinued in accordance with standard of care.

If therapy in Crohn's disease is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.

Dosage – (Pediatric population, 6 years and older)

Plaque Psoriasis

For the treatment of plaque psoriasis, Ustekinumab (Stelara®) should be administered by subcutaneous injection. The recommended dose of Ustekinumab (Stelara®) based on body weight is shown below (Table 34). Ustekinumab (Stelara®) should be administered at Weeks 0 and 4, then every 12 weeks thereafter.

Table 34: Recommended dose of Ustekinumab (Stelara®) for pediatric psoriasis

Weight	Recommended Dose	Dosage Form
< 60 kg	0.75 mg/kg*	vial
≥ 60 to ≤ 100 kg	45 mg	Pre-filled syringe, vial
> 100 kg	90 mg	Pre-filled syringe, vial

* To calculate the volume of injection (mL) for patients < 60 kg, use the following formula: *body weight* (kg) × *0.0083* (mL/kg). The calculated volume should be rounded to the nearest 0.01 mL and administered using a 1 mL graduated syringe. A 45 mg vial is available for pediatric patients who need to receive less than the full 45 mg dose.

Table 34b Injection volumes of Ustekinumab (Stelara®) for pediatric psoriasis patients < 60 kg

Body weight at time of dosing (kg)	Dose (mg)	Volume of injection (mL)
15	11.3	0.12
16	12.0	0.13
17	12.8	0.14
18	13.5	0.15
19	14.3	0.16
20	15.0	0.17
21	15.8	0.17
22	16.5	0.18
23	17.3	0.19
24	18.0	0.20
25	18.8	0.21
26	19.5	0.22
27	20.3	0.22
28	21.0	0.23
29	21.8	0.24
30	22.5	0.25
31	23.3	0.26
32	24.0	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27.0	0.30
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30.0	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33.0	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36.0	0.40
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39.0	0.43

53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42.0	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

General Consideration for Administration

Subcutaneous administration

Ustekinumab (Stelara®) is intended for use under the guidance and supervision of a physician. In pediatric patients, it is recommended that Ustekinumab (Stelara®) be administered by a health care provider. A patient may self-inject with Ustekinumab (Stelara®) if a physician determines that it is appropriate and with medical follow-up as necessary, after proper training in subcutaneous injection technique and disposal (see ***Instructions for Use, Handling and Disposal***).

Patients should be instructed to inject the prescribed amount of Ustekinumab (Stelara®) according to the directions provided in the patient information leaflet. The needle cover on the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Intravenous infusion (Crohn's Disease and Ulcerative Colitis)

Ustekinumab (Stelara®) 130 mg vial is for IV infusion only. Intravenous infusion of Ustekinumab (Stelara®) should be administered by qualified health care professionals (For preparation, see ***Instructions for Use, Handling and Disposal***).

Special populations

Pediatrics

Studies of Ustekinumab (Stelara®) in pediatric patients below 6 years of age have not been conducted. No studies have been conducted in pediatric patients with psoriatic arthritis, Crohn's disease or ulcerative colitis.

Elderly

Of the 6709 patients exposed to Ustekinumab (Stelara®), a total of 353 were 65 years or older (183 patients with psoriasis, 69 patients with psoriatic arthritis, 58 with Crohn's disease, and 43 patients with ulcerative colitis). No major age-related differences in clearance or volume of distribution were observed in clinical studies. Although no overall differences in safety or efficacy were observed between older and younger patients in clinical studies in approved indications, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

Renal impairment

Specific studies have not been conducted in patients with renal insufficiency.

Hepatic impairment

Specific studies have not been conducted in patients with hepatic insufficiency.

CONTRAINDICATIONS
Severe hypersensitivity to ustekinumab or to any of the excipients (see ***Special Warnings and Special Precautions for Use***).

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
Infections
Ustekinumab (Stelara®) is a selective immunosuppressant and may have the potential to increase the risk of infections and reactivate latent infections.

In clinical studies, serious bacterial, fungal, and viral infections have been observed in patients receiving Ustekinumab (Stelara®).

Ustekinumab (Stelara®) should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of Ustekinumab (Stelara®) in patients with a chronic infection or a history of recurrent infection.

Prior to initiating treatment with Ustekinumab (Stelara®), patients should be evaluated for tuberculosis infection. Ustekinumab (Stelara®) should not be given to patients with active tuberculosis. Treatment of latent tuberculosis infection should be initiated prior to administering Ustekinumab (Stelara®). Anti-tuberculosis therapy should also be considered prior to initiation of Ustekinumab (Stelara®) in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving Ustekinumab (Stelara®) should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection they should be closely monitored and Ustekinumab (Stelara®) should not be administered until the infection resolves (see ***Undesirable Effects***).

Malignancies
Ustekinumab (Stelara®) is a selective immunosuppressant. Immunosuppressive agents have the potential to increase the risk of malignancy. Some patients who received Ustekinumab (Stelara®) in clinical studies developed cutaneous and noncutaneous malignancies (see ***Undesirable Effects***).

Ustekinumab (Stelara®) has not been studied in patients with a history of malignancy. Caution should be exercised when considering the use of Ustekinumab (Stelara®) in patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of non-melanoma skin cancer (see ***Undesirable Effects***).

Hypersensitivity reactions
In post-marketing experience, serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported. If an anaphylactic or other serious hypersensitivity reaction occurs, institute appropriate therapy and administration of Ustekinumab (Stelara®) should be discontinued (see ***Undesirable Effects***).

Immunizations
It is recommended that live viral or live bacterial vaccines not be given concurrently with Ustekinumab (Stelara®).

No data are available on the secondary transmission of infection by live vaccines in patients receiving Ustekinumab (Stelara®). Caution is advised when administering some live vaccines to household contacts of patients receiving Ustekinumab (Stelara®) because of the potential risk for shedding from the household contact and transmission to the patient.

Patients receiving Ustekinumab (Stelara®) may receive concurrent inactivated or non-live vaccinations.

Long term treatment with Ustekinumab (Stelara®) does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see ***Pharmacodynamic Properties***).

Infant exposure in utero
For infants exposed *in utero* to ustekinumab, a six month waiting period following birth is recommended before the administration of live vaccines. Administration of a live vaccine prior to 6 months of age may be considered if ustekinumab dosing was limited to the first trimester of pregnancy when placental transport is minimal, or ustekinumab serum levels are undetectable in the infant, or the benefit of the vaccination clearly outweighs the theoretical risk of administration of live vaccines to the infant (see ***Pregnancy, Breast-feeding and Fertility***).

Immunosuppression
In psoriasis studies, the safety and efficacy of Ustekinumab (Stelara®) in combination with immunosuppressive agents or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of Ustekinumab (Stelara®). In Crohn's disease and ulcerative colitis studies, concomitant use of immunomodulators (6-mercaptopurine (6-MP), azathioprine (AZA), MTX) or corticosteroids did not appear to influence the safety or efficacy of Ustekinumab (Stelara®). Caution should be exercised when considering concomitant use of immunosuppressive agents and Ustekinumab (Stelara®) or when transitioning from other biologic agents.

Immunotherapy
Ustekinumab (Stelara®) has not been evaluated in patients who have undergone allergy immunotherapy. Ustekinumab (Stelara®) may affect allergy immunotherapy. Caution should be exercised in patients receiving or who have received allergy immunotherapy particularly for anaphylaxis.

General
The needle cover on the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

- Drug interaction studies have not been conducted in humans with Ustekinumab (Stelara®) (see ***Pharmacokinetic Properties***).

- The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4). These results

do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see ***Pharmacokinetic Properties***).

- Live vaccines should not be given concurrently with Ustekinumab (Stelara®). Recommendations for infants exposed to ustekinumab *in utero* are provided (see ***Special Warnings and Special Precautions for Use***).

PREGNANCY, BREAST-FEEDING AND FERTILITY

Pregnancy

There is no evidence from animal studies of teratogenicity, birth defects or developmental delays at exposures up to approximately 150-fold higher compared to C_{max} following 4 weekly 90 mg subcutaneous injections or up to 21-fold higher compared to serum concentrations 1 h following 6 mg/kg IV administration (see ***Non-Clinical Information***). However, animal reproductive and developmental studies are not always predictive of human response.

It is not known whether Ustekinumab (Stelara®) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ustekinumab (Stelara®) should be given to a pregnant woman only if the benefit clearly outweighs the risk.

Breast-feeding

Limited data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts. While systemic exposure to a breastfed infant is expected to be low because ustekinumab is a large molecule is degraded in the gastrointestinal tract, it is not known if Ustekinumab (Stelara®) is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from Ustekinumab (Stelara®), a decision should be made whether to discontinue nursing or to discontinue the drug.

Fertility

The effect of Ustekinumab (Stelara®) on human fertility has not been evaluated. No adverse effects on female fertility parameters were identified in a female fertility toxicity study conducted in mice (see ***Non-Clinical Information***).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

UNDESIRABLE EFFECTS

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of ustekinumab based on the comprehensive assessment of the available adverse event information. A causal relationship with ustekinumab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Studies Experience in Adult Patients with Psoriasis, Psoriatic Arthritis, Crohn's Disease, and Ulcerative Colitis

The safety data described below reflect exposure to Ustekinumab (Stelara®) in 14 Phase 2 and Phase 3 studies in 6709 patients (4135 with psoriasis and/or psoriatic arthritis, 1749 for Crohn's disease, and 825

with ulcerative colitis in UC-1 and UC-2 clinical trials), with duration of exposure to Ustekinumab (Stelara®) presented in Table 35.

Table 35: Long term exposure to Ustekinumab (Stelara®) in Phase 2 and Phase 3 clinical studies	
Exposure	**Number of patients**
6 months	4577[a]
1 year	3253[a]
≥ 4 years	1482[b]
≥ 5 years	838[b]

[a] Total number of patients in the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis studies
[b] Number of patients with psoriasis

The most common adverse reactions (>5%) in controlled periods of the clinical studies with Ustekinumab (Stelara®) among all indications were nasopharyngitis and headache. Most were considered to be mild and did not necessitate drug discontinuation. The overall safety profile of Ustekinumab (Stelara®) was similar for patients among all indications.

Table 36 provides a summary of Adverse Reactions from the clinical studies. The frequency of these adverse reactions was based on those that occurred during the initial controlled periods of the clinical studies. The adverse reactions are ranked by frequency, using the following convention:

Very common (≥1/10)
Common (frequent) (≥1/100, <1/10)
Uncommon (infrequent) (≥1/1000, <1/100)
Rare (≥1/10000, <1/1000)

Table 36: SUMMARY OF ADVERSE REACTIONS IN CLINICAL STUDIES	
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, viral upper respiratory tract infection, vulvovaginal mycotic infection
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion
Gastrointestinal disorders	Common: Diarrhea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Acne
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including hemorrhage, hematoma, induration, swelling and pruritus), asthenia

Infections
In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's Disease and ulcerative colitis, the rates of infection or serious infection were similar between Ustekinumab (Stelara®)-treated patients and those treated with placebo. In the placebo-controlled period of clinical studies of patients with psoriasis, patients with psoriatic arthritis, patients with Crohn's disease, and patients with ulcerative colitis, the rate of infection was 1.36 per patient-year of follow-up in Ustekinumab (Stelara®)-treated patients, and 1.34 per patient-year of follow-up in placebo-treated patients. Serious infections occurred at a rate of 0.03 per patient-year of follow-up in Ustekinumab (Stelara®)-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 per patient-year of follow-up in placebo-treated patients (15 serious infections in 434 patient-years of follow-up) (see ***Special Warnings and Special Precautions for Use***).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, clinical studies representing 11581 patient-years of exposure in 6709 patients, the median follow-up was 1.0 years; 1.1 years for psoriatic disease studies, and 0.6 year for Crohn's disease studies, and 1.0 years for ulcerative colitis studies. The rate of infection was 0.91 per patient-year of follow-up in Ustekinumab (Stelara®)-treated patients. The rate of serious infections was 0.02 per patient-year of follow-up in Ustekinumab (Stelara®)-treated patients (199 serious infections in 11581 patient-years of follow-up) and included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis and viral infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

Malignancy
In the placebo-controlled period of the psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for Ustekinumab (Stelara®)-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 per 100 patient-years of follow-up for placebo-treated patients (1 patient in 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for Ustekinumab (Stelara®)-treated patients (4 patients in 929 patient-years of follow-up) compared with 0.46 per 100 patient-years of follow-up for placebo-treated patients (2 patients in 433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulceratie colitis clinical studies representing 11561 patient-years of exposure in 6709 patients, the median follow-up was 1.0 years; 1.1 years for psoriatic disease studies, 0.6 year for Crohn's disease studies, and 1.0 years for ulcerative colitis studies. Malignancies, excluding non-melanoma skin cancers, were reported in 62 patients in 11561 patient-years of follow-up (incidence of 0.54 per 100 patient-years of follow-up for Ustekinumab (Stelara®)-treated patients). The incidence of malignancies, reported in Ustekinumab (Stelara®)-treated patients was comparable to the incidence expected in the general population (standardized incidence ratio = 0.93 [95% confidence interval: 0.71, 1.20], adjusted for age, gender and race)[1]. The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, colorectal, melanoma, and breast. The incidence of non-melanoma skin cancer was 0.49 per 100 patient-years of follow-up for Ustekinumab (Stelara®)-treated patients (56 patients in 11545 patient-years of follow-up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is

comparable with the ratio expected in the general population (see ***Special Warnings and Special Precautions for Use***).

[1]Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 6.6.2 Regs Research Data, Nov 2009 Sub (1973-2007) - Linked To County Attributes - Total U.S., 1969-2007 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2010, based on the November 2009 submission.

Hypersensitivity and Infusion Reactions

Subcutaneous administration

During the controlled periods of the psoriasis and psoriatic arthritis clinical studies of Ustekinumab (Stelara®), rash and urticaria have each been observed in <1% of patients.

IV administration

In Crohn's disease and ulcerative colitis intravenous induction studies, no events of anaphylaxis or other serious infusion reactions were reported. In Crohn's disease studies, 2.4% of 466 placebo treated patients and 2.6% of 470 patients treated with the recommended dose of Ustekinumab (Stelara®) reported adverse events occurring during or within an hour of the infusion. In ulcerative colitis studies, 1.9% of 319 placebo patients and 0.9% of 320 patients treated with the recommended dose of Ustekinumab (Stelara®) reported adverse events occurring during or within an hour of the infusion.

Immunogenicity

In psoriasis and psoriatic arthritis clinical studies, up to 12.4% of patients treated with Ustekinumab (Stelara®) developed antibodies to ustekinumab. Patients positive for antibodies to ustekinumab tended to have lower efficacy, however, antibody positivity did not preclude a clinical response. The majority of patients who were positive for antibodies to ustekinumab had neutralizing antibodies. In Crohn's disease and ulcerative colitis clinical studies, 2.9% and 4.6% of patients, respectively, developed antibodies to ustekinumab when treated with ustekinumab for approximately one year. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was observed.

OVERDOSE

Single doses up to 6 mg/kg intravenously have been administered in clinical studies without dose-limiting toxicity. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

Clinical Studies Experience in pediatric patients with Psoriasis

The safety of Ustekinumab (Stelara®) has been studied in two phase 3 studies of pediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks (CADMUS) and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks (CADMUS Jr.). In general, the adverse events reported in these two studies were similar to those seen in previous studies in adults with plaque psoriasis. (see ***Clinical Studies Experience in Adult Patients with Psoriasis and/or Psoriatic Arthritis*** section above).

Post Marketing Experience

The adverse reactions in Table 37 are ranked by frequency* using the following convention:

Very common: ≥1/10

Common: ≥1/100 and <1/10
Uncommon: ≥1/1000 and <1/100
Rare: ≥1/10000 and <1/1000
Very rare: <1/10000, including isolated reports

Table 37: Post-Marketing Reports	
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis and angioedema)
Infections and infestations	Uncommon: Lower respiratory tract infection
Respiratory, thoracic and mediastinal disorders	Rare: Allergic alveolitis, eosinophilic pneumonia
Skin and subcutaneous tissue disorders	Uncommon: Pustular psoriasis Rare: Erythrodermic psoriasis

*Post-marketing adverse reaction frequency is derived from the placebo-controlled portion of the 11 clinical trials if the adverse reaction was observed in those trials. Otherwise, it is estimated to be lower than a certain frequency given the exposure in the 11 clinical trials where the adverse reaction was not observed.

INCOMPATIBILITIES
Not applicable.

STORAGE CONDITIONS
Store in a refrigerator (2-8°C).
Store in original carton until time of use.
Protect from light. Do not freeze. Do not shake.
Keep out of the sight and reach of children.

INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL
Following administration of Ustekinumab (Stelara®), discard any unused portion. The syringe should be disposed of with accepted medical practices for used syringes. The syringe, needle and vial must never be re-used.

Instructions for dilution of Ustekinumab (Stelara®) 130 mg for IV infusion (Crohn's disease)
Ustekinumab (Stelara®) 130 mg solution must be diluted and prepared for IV infusion by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of Ustekinumab (Stelara®) vials needed based on patient's body weight (see Table 33). Each 26 mL vial of Ustekinumab (Stelara®) contains 130 mg of ustekinumab.
2. Withdraw and then discard a volume of the 0.9% w/v sodium chloride solution from the 250 mL infusion bag equal to the volume of Ustekinumab (Stelara®) to be added. (discard 26 mL sodium chloride for each vial of Ustekinumab (Stelara®) needed, for 2 vials-discard 52 mL, for 3 vials-

discard 78 mL, for 4 vials- discard 104 mL). Alternatively, a 250 mL infusion bag containing 0.45% w/v sodium chloride solution may be used.
3. Withdraw 26 mL of Ustekinumab (Stelara®) from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Visually inspect the diluted solution before administration. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
5. Administer the diluted solution over a period of at least one hour. Once diluted, the infusion should be completed within eight hours of the dilution in the infusion bag.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).
7. Do not infuse Ustekinumab (Stelara®) concomitantly in the same intravenous line with other agents.
8. Each vial is for single use only and any unused medicinal product should be disposed of in accordance with local requirements.

Storage

If necessary, the diluted infusion solution may be stored at room temperature. The infusion should be completed within 8 hours of the dilution in the infusion bag. Do not freeze. Discard any unused portion of the infusion solution.

NATURE AND CONTENTS OF CONTAINERS

For subcutaneous injection

Ustekinumab (Stelara®) is supplied as a sterile solution in a single-use (Type 1) glass vial. The vial is stoppered with a coated stopper.

Ustekinumab (Stelara®) is supplied as a single-use, sterile solution in a Type 1 glass syringe with a fixed 27G, half-inch needle and needle cover. The needle cover is manufactured using a dry natural rubber (a derivative of latex), (see ***Special Warnings and Special Precautions for Use*****).** The syringe is fitted with a passive safety guard.

For intravenous infusion only

Ustekinumab (Stelara®) 130 mg vial is supplied as a sterile solution in a single-use (Type 1) glass vial. The vial is stoppered with a coated stopper.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Patient must seek medical attention immediately at the first sign of any adverse drug reaction. For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.

Questions or comments? Email us at Janssendrugsafety_Phil@its.jnj.com.

AVAILABILITY

45 mg/0.5 mL pre-filled syringe
90 mg/mL pre-filled syringe
130 mg/26 mL vial
45 mg/0.5 mL vial

REGISTRATION NUMBER

Stelara 45 mg/0.5 mL (pre-filled syringe): BR-1287
Stelara 90 mg/mL: BR-983
Stelara 130 mg/26 mL: BR-1311
Stelara 45 mg/0.5 mL (vial): BR-1415

DATE OF FIRST AUTHORIZATION
Stelara 45 mg/0.5 mL (pre-filled syringe): 13 October 2010
Stelara 90 mg/mL: 14 October 2014
Stelara 130 mg/26 mL: 02 April 2020
Stelara 45 mg/0.5 mL (vial): 31 August 2022

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