



## **Briefing Document for Ustekinumab (CNTO 1275)**

**Food and Drug Administration  
Dermatologic and Ophthalmic Drugs Advisory Committee  
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## Abbreviations

AE	adverse event
AUC	area under the serum concentration-versus-time curve
BCG	Bacille Calmette-Guerin
BLA	Biological License Application
BMI	body mass index
BSA	body surface area
CDC	Centers for Disease Control
CI	confidence interval
CLA	cutaneous lymphocyte antigen
C <sub>max</sub>	maximum concentration of drug
DLQI	Dermatology Life Quality Index
EFD	embryofetal development
FDA	Food and Drug Administration
GPRD	General Practice Research Database
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS anxiety scale
HADS-D	HADS depression scale
Hb A <sub>1c</sub>	glycosylated hemoglobin
HDL	high-density lipoprotein
ICH	International Conference on Harmonisation
IFN $\gamma$	interferon gamma
IgG	immunoglobulin gamma
IL	interleukin
IL-12R $\beta$ 1	interleukin 12 receptor beta 1
IL-23R	interleukin 23 receptor
IV	intravenous
$\kappa$	kappa
KC	keratinocyte
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MS	multiple sclerosis
MTX	methotrexate
NA	not applicable
NAPSI	Nail Psoriasis Severity Index
NCEP	National Cholesterol Education Program
NK	natural killer
NMSC	nonmelanoma skin cancer
nonresponders	subjects with < 50% improvement in PASI from baseline
partial responders	subjects with $\geq$ 50% and < 75% improvement in PASI from baseline
PASI	Psoriasis Area and Severity Index
PASI 50 responders	subjects with $\geq$ 50% improvement in PASI from baseline
PASI 75 responders	subjects with $\geq$ 75% improvement in PASI from baseline
PASI 90 responders	subjects with $\geq$ 90% improvement in PASI from baseline
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic

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PGA	Physician's Global Assessment (of disease severity)
PK	pharmacokinetic
PPD	purified protein derivative
PsA	psoriatic arthritis
PSOLAR	PSoriasis Longitudinal Assessment and Registry
PUVA	psoralen plus ultraviolet A light
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results
SF-36	36-item short form health survey
SIR	standardized incidence rate (ratio)
SMR	standardized mortality ratio
STAT	signal transducers and activators of transcription
TB	tuberculosis
Th	T helper cells
TC/HDL	total cholesterol/high-density lipoprotein (ratio)
TNF $\alpha$	tumor necrosis factor alpha
TC	total cholesterol
US	United States
USPI	United States Package Insert
VAS	visual analog scale
WLQ	Work Limitations Questionnaire

## Purpose of Document

The purpose of this document is to provide background information on the development program for ustekinumab (CNTO 1275) in the treatment of adults with moderate to severe plaque psoriasis and to review the efficacy and safety data that support the approval of the product in the target indication.

## Regulatory History

The ustekinumab development program has been designed in accordance with applicable FDA and ICH regulatory guidelines. Centocor has also sought feedback from the FDA at key milestones during the development process. Importantly, the Phase 3 confirmatory studies were designed in collaboration with the FDA. During discussions at the End of Phase 2 meeting, Centocor received substantial feedback from the FDA on study design, including:

- The need to evaluate the safety and efficacy of long term continuous use, response off treatment, and potential for rebound, which led to incorporation of a randomized withdrawal design to evaluate each of these issues;
- The need to evaluate the response to retreatment, which was included in one of the Phase 3 studies;
- The need to consider discontinuation of treatment in nonresponders (included in both Phase 3 studies) and possible study of alternate dosing (eg, dose escalation) in subjects who partially, but incompletely, respond, which led to study of dosing optimization in partial responders;
- The number of regimens originally proposed may risk insufficient data to support a specific regimen, which led to evaluating 2 dosing regimens only;
- The need to study self-administration during a controlled period of the trial, which led to its study in a controlled portion of one of the Phase 3 studies.

Centocor filed a Biological License Application (BLA) for the use of ustekinumab in the treatment of adults with moderate to severe plaque psoriasis.

# 1 Executive Summary

Ustekinumab is a novel therapeutic for the treatment of chronic, moderate to severe plaque psoriasis. It is a fully human monoclonal antibody that binds to the shared p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23). It is thought to act by preventing these cytokines from differentiating and activating T helper (Th)1 and Th17 cells, thereby inhibiting key pathways implicated in the immunopathogenesis of psoriasis.

Three adequate, well-controlled studies of ustekinumab using 45 mg or 90 mg dosing regimens in subjects with moderate to severe plaque psoriasis consistently demonstrated that ustekinumab was highly effective in ameliorating psoriatic plaques, pruritus, and nail psoriasis, and improving patient-reported outcomes as evaluated by multiple measures.

These studies met the primary and all major secondary endpoints. In the Phase 3 studies:

- High proportions of subjects in both ustekinumab dosing groups (66.4% to 75.7%) achieved a Psoriasis Area and Severity Index 75 (PASI 75) response at Week 12 (the primary endpoint) compared with 3 to 4% of placebo-treated subjects.
- The high level of efficacy was substantiated by the Physician Global Assessment (PGA) of psoriasis (60.4% to 73.5% with a PGA of cleared or minimal compared with 4 to 5% for placebo).
- Significant, clinically meaningful improvements were observed as measured by the patient-reported Dermatology Life Quality Index (DLQI; mean reduction in DLQI score of 8.0 to 10.0 for ustekinumab groups versus 0.5 to 0.6 for placebo).
- PASI 75 response was generally maintained through at least 1 year in subjects receiving every 12 weeks maintenance therapy. This maintenance was significantly superior to that observed in subjects withdrawn from ustekinumab ( $p < 0.001$  by log rank test). Through Week 52, a PASI 75 response was maintained in 87.0% of subjects on every 12 weeks maintenance therapy compared with 61.7% of subjects withdrawn from therapy (ie, 12 weeks after 1 missed dose) based on life-table estimates.

Other measures of efficacy showed that:

- Ustekinumab had high efficacy at Week 12 measured by a variety of PASI and PGA thresholds, with more than 80% of subjects achieving PASI 50 versus approximately 10% for placebo; 37 to 51% achieving PASI 90 versus 1 to 2% for placebo; and 85 to 92% achieving a PGA of cleared, minimal, or mild versus 18 to 21% for placebo.

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- Onset of efficacy was rapid. At Week 4, a significantly greater proportion of subjects in each dosing group achieved a PASI 75 response (9 to 20%) compared with placebo (< 1%).
  - Ustekinumab consistently demonstrated high levels of efficacy in all subpopulations including subgroups defined by demographics, disease characteristics, and previous therapies.
  - An association between clinical response and serum concentrations was observed.
  - In subjects > 100 kg, efficacy and serum concentrations were lower in those who received 45 mg compared to 90 mg. Subjects > 100 kg who received 90 mg had similar serum concentration to subjects ≤ 100 kg who received 45 mg.

Based on safety analyses in 2266 ustekinumab-treated subjects with moderate to severe plaque psoriasis, ustekinumab appears to be safe and well tolerated.

- Common adverse events occurred at similar rates in ustekinumab- and placebo-treated subjects, and were generally mild and self-limited. Rates of adverse events did not increase with increasing dose, with duration of exposure, or with increasing cumulative exposure.
- Serious adverse events occurred at generally similar rates between ustekinumab- and placebo-treated subjects.
- Rates of serious infections and malignancies were low and similar between ustekinumab- and placebo-treated subjects; the observed rates were consistent with the expected background rates.
- A numeric imbalance in rates of major adverse cardiovascular events was observed between ustekinumab- and placebo-treated subjects during the placebo-controlled portion of the Phase 2 study. The degree of imbalance was not seen in the larger Phase 3 program and was attenuated with the pooling of the Phase 2 and Phase 3 data. There was no evidence of increased cardiovascular events when the analysis was extended through the data cutoff for the BLA.
- No adverse impact on psoriasis (eg, evidence of rebound psoriasis) or psoriatic arthritis (PsA) was observed.
- No evidence of lymphocyte depletion or cumulative dosing toxicities was observed.

## 1.1 Proposed Indication

Ustekinumab is indicated for the treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

## 1.2 Efficacy

The psoriasis clinical development program of ustekinumab consisted of 3 well-controlled Phase 2 (T04) and Phase 3 (T08 and T09) clinical studies in subjects with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy. T08 and T09 have ongoing long-term extensions, which will provide 5 years of data to evaluate the long-term safety and efficacy of ustekinumab. Supportive information is provided by two Phase 1 studies in psoriasis, which evaluated single intravenously or subcutaneously administered doses.

The Phase 2 and Phase 3 studies evaluated treatment with ustekinumab (45 mg or 90 mg) as monotherapy. Adults who had moderate to severe plaque psoriasis defined as  $\geq 10\%$  of total body surface area and a PASI score of  $\geq 12$  and who were candidates for phototherapy or systemic therapy were enrolled. The primary efficacy endpoint in these studies was the proportion of subjects with a PASI 75 response at Week 12.

Two Phase 3 studies consistently demonstrated that ustekinumab was highly effective. Treatment with ustekinumab led to rapid, clinically significant, and substantial improvements in psoriasis. The degree of efficacy demonstrated in these studies is consistent with the highest degree of efficacy demonstrated with conventional systemic agents and biologics. Ustekinumab was effective across all subpopulations. Efficacy was similar in subgroups defined by disease severity, other disease characteristics, or previous use of phototherapy or other systemic agents. This breadth and magnitude of response were consistently observed using a variety of disease measures, and were observed in skin and also in nail psoriasis (assessed by Nail Psoriasis Severity Index), which is often difficult to treat. In addition, the efficacy was consistent whether ustekinumab was self-administered or health care professional-administered.

Disease-specific (DLQI and Itch Visual Analogue Scale [VAS]) and general patient-reported (36-item short form health survey [SF-36], Hospital Anxiety and Depression Scale [HADS], Work Limitations Questionnaire [WLQ], Productivity VAS) outcome measures showed statistically significant and clinically meaningful improvements with ustekinumab treatment. Significant and substantial improvements were observed in pruritus itch (Itch VAS), the DLQI, and SF-36 among subjects receiving ustekinumab. Subjects receiving ustekinumab reported significantly less anxiety and depression (measured by HADS) as well as less impairment and increased productivity at work (WLQ and Productivity VAS). Over one-third of ustekinumab-treated subjects indicated that psoriasis had no detectable impairment on their quality of life during active treatment (as reflected by DLQI = 0).

Results from the randomized withdrawal portion of the T08 study demonstrated that maintaining psoriasis control after Week 40 required continued treatment with ustekinumab. Significantly superior maintenance of PASI 75 response was observed through at least 1 year in subjects receiving every 12 weeks maintenance therapy compared with subjects withdrawn from ustekinumab at Week 40 ( $p < 0.001$  by log rank test; a major secondary endpoint). Clinical response was maintained with every 12 weeks administrations of ustekinumab through 1 year in nearly 90% of long-term PASI 75 responders. In subjects withdrawn from drug, psoriasis recurrence was observed as early as 4 weeks after a missed dose, and continued to progressively decline over time.

An association between clinical response and serum concentrations was observed, and serum concentrations were impacted by weight. In subjects  $> 100$  kg, the 90 mg regimen provided efficacy levels approximately 15 to 20 percentage points higher than those subjects  $> 100$  kg in the 45 mg regimen as measured by PASI 75 response at Week 12 in Phase 3 studies (49 to 54% PASI 75 for the 45 mg groups versus 68 to 71% for the 90 mg groups). Use of this higher dose in patients  $> 100$  kg may serve a significant unmet need.

### 1.3 Safety

A total of 2266 subjects have been treated with ustekinumab through the data cutoff for the BLA in Phase 2 and Phase 3 psoriasis studies (T04, T08, and T09). Of these, 1582 subjects received ustekinumab during the placebo-controlled periods, with a common placebo-controlled period of 12 weeks in duration. Long-term safety findings submitted in the BLA was supported by data from 1602 subjects who received at least 6 months of ustekinumab treatment and 362 subjects exposed for at least 1 year. In the 120-day safety update, 1970 subjects were exposed for at least 6 months, 1285 exposed for at least 1 year, and 373 exposed for at least 18 months.

- The proportions of subjects who experienced at least 1 adverse event through Week 12 were 50.4% in the placebo group, 57.6% in the 45 mg group, and 51.6% in the 90 mg group. Infections and infestations were the most frequently reported class of adverse events, and were reported in 23.0% of subjects in the placebo group, 26.6% in the 45 mg group, and 25.1% in the 90 mg group. Common adverse events tended to be mild and self-limited. The proportions of subjects who discontinued study agent because of an adverse event was low through Week 12 (1.9%, 1.1%, and 1.4% in the placebo, 45 mg, and 90 mg groups, respectively).
- Serious adverse events were reported in 1.4 %, 1.6%, and 1.4% in the placebo, 45 mg, and 90 mg groups, respectively, through Week 12. Most events occurred in only 1 subject in any treatment group, with the exception of cellulitis, which occurred in 2 (0.3%) subjects in the placebo group and 2 (0.3%) subjects in the 90 mg group, and intervertebral disc protrusion, which occurred in 2 (0.3%) subjects in the 45 mg group.

- Rates of adverse events and serious adverse events did not increase with duration of exposure. No adverse impact on psoriasis (eg, evidence of rebound psoriasis) or psoriatic arthritis was observed. No evidence of lymphocyte depletion or cumulative dosing toxicities was observed. Safety of ustekinumab was consistent in all subpopulations based on demographics (eg, weight and age), and safety was generally comparable between subjects who self-administered ustekinumab and those in whom it was administered by a health care professional.

Through the controlled portions of the studies, serious infections were reported at a rate of 1.70 (95% confidence interval [CI], 0.35, 4.96) per hundred subject-years of follow-up in placebo-treated subjects compared with 0.49 (95% CI, 0.01, 2.74) and 1.97 (95% CI, 0.54, 5.03) in subjects in the 45 mg and 90 mg ustekinumab groups, respectively (with a rate of 1.23 [95% CI, 0.40, 2.87] in the combined ustekinumab group). Overall rates of serious infections per hundred subject-years of follow-up in ustekinumab-treated subjects remained stable or decreased slightly through the data cutoff for the BLA (1.02 [95% CI, 0.57, 1.69]).

During the placebo-controlled portions of the psoriasis clinical studies, malignancies were reported in 3 placebo-treated subjects and 4 ustekinumab-treated subjects (2 each in the 45 mg and 90 mg groups). Three of the 4 malignancies reported in ustekinumab-treated subjects and 2 of the 3 malignancies reported in placebo-treated subjects were nonmelanoma skin cancers. Overall rates of malignancies per hundred subject-years of follow-up were comparable between placebo-treated subjects (1.70 [95% CI, 0.35, 4.98]) and ustekinumab-treated subjects (0.99 [95% CI, 0.27, 2.52]). Overall rates of malignancies per hundred subject-years of follow-up in ustekinumab-treated subjects remained stable through the data cutoff for the BLA (1.30 [95% CI, 0.78, 2.03]).

In the pooled Phase 2 and 3 psoriasis data, 5 major adverse cardiovascular events (cardiovascular death, myocardial infarction [MI], or stroke) were reported in combined ustekinumab-treated subjects during the placebo-controlled portions of the psoriasis clinical studies (rate 1.23 [95% CI 0.40 – 2.87]). Three of the 5 events occurred in the Phase 2 study, which had an imbalanced 4:1 ustekinumab to placebo randomization. No major adverse cardiovascular events were reported in placebo-treated subjects during the placebo-controlled portions of the psoriasis clinical studies (although one placebo-only treated subject [who never crossed over to ustekinumab therapy] experienced an MI 3 days after the end of the controlled portion). Through the data cutoff for the BLA, the rates of major adverse cardiovascular events per hundred subject-years of follow-up were comparable between placebo-treated and ustekinumab-treated subjects, 0.55 (95% CI 0.01 – 3.06) versus 0.61 (95% CI 0.28 – 1.16), respectively. Rates of major adverse cardiovascular events were consistent with expected background rates.

The incidence of antibodies to ustekinumab was low and similar across all psoriasis studies despite differences in doses, schedules and routes of administration, formulations, and study intervals. The overall incidence of antibodies to ustekinumab in the combined Phase 3 psoriasis studies was 3.7%. Antibody titers in the Phase 3 studies were generally



low with the majority (66.2%) being  $\leq 1:80$ . Titer did not differ across doses, and the incidence of antibodies to ustekinumab did not appear to increase over time.

With incremental safety data available since the initial BLA and submitted in the 120-day safety update, the safety profile was consistent with the safety data submitted in the initial BLA. Rates of adverse events, serious adverse events, serious infections, malignancies and serious cardiovascular events, when adjusted for follow-up, did not increase with time.

A Risk Management Plan has been proposed that will enhance our understanding of the potential safety issues and minimize risk. The comprehensive plan includes active and passive surveillance, disease and pregnancy registries with comparator data, labeling, and physician and patient educational programs.

## **1.4 Conclusions**

Ustekinumab is a safe and effective treatment for subjects with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Ustekinumab was highly effective and treatment led to rapid, clinically significant, and substantial improvements in psoriasis, and clinical response was maintained with every 12 week dosing. Rates of serious infections, malignancies, and serious cardiovascular events were low and consistent with the expected background rates.

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## 2 Therapeutic Rationale

### 2.1 Psoriasis

Psoriasis is a life-long, immune-mediated inflammatory skin disease of unknown etiology, affecting up to 3% of the general population, with rates varying among geographic areas and races ([Krueger and Duvic, 1994](#)). Of these, 80% of patients have chronic plaque psoriasis, characterized by recurrent exacerbations and remissions of thickened, erythematous, scaly patches of skin that can occur anywhere on the body. Patients with moderate to severe disease represent approximately 15% to 25% of plaque psoriasis patients, and these patients often require treatment with phototherapy and/or systemic therapy for adequate control of their disease ([Stern et al, 2004](#); [Sterry et al, 2004](#)). Psoriatic symptoms can cause physical discomfort (pain and pruritus), and when combined with the psychological effects of the disease often interfere with everyday activities and negatively impact a patient's quality of life. In addition to the physical and psychological impact of disease, psoriasis is also associated with multiple comorbidities, including psoriatic arthritis (PsA), depression, cardiovascular disease, hypertension, obesity, diabetes, metabolic syndrome, smoking, and Crohn's disease. Recently the National Psoriasis Foundation issued a clinical consensus on the comorbidities found in psoriasis patients and provided clinicians with recommendations for screening ([Kimball et al, 2008](#)).

#### 2.1.1 Approved Systemic Therapies and Unmet Need

A list of FDA-approved systemic agents (including biologics) for the treatment of psoriasis is presented in Table 1. This summary includes, where available, the efficacy and safety (warnings and precautions) included in each product's prescribing information. While there are many available treatments, these agents each have significant side effects. Currently approved small molecule systemic agents (methotrexate [MTX], cyclosporine, and acitretin) have safety limitations, including organ toxicity, infection, malignancy, and teratogenicity that limit their usefulness in the long-term management of psoriasis. Psoralen plus ultraviolet A light (PUVA) is associated with an increased risk of skin malignancies, imposes significant lifestyle restrictions on patients with frequent visits to specialized phototherapy units and is not suitable for continuous long-term chronic psoriasis management because of cumulative photo-damage. While 5 biologic agents have been approved for the treatment of psoriasis, some have limited and/or diminishing efficacy, most require at least weekly administration, and each may be accompanied by drug-specific safety concerns (eg, infection including tuberculosis (TB), malignancies including lymphoma, and demyelinating neurologic events). Thus, there remains a significant unmet need for a therapy that will provide high continuous efficacy, an improved safety profile, and a more convenient dosing schedule to maximize patient adherence and treatment satisfaction.

<b>Table 1      Summary of FDA-approved systemic therapies for the treatment of psoriasis</b>			
<b>Therapy (Year of Approval)</b>	<b>Indications</b>	<b>Efficacy (Dose Regimen used in Clinical Studies)</b>	<b>Safety/Tolerability (Warning and Precaution Section)</b>
<b>Methotrexate (prior to 1999)</b>	Severe, recalcitrant, disabling psoriasis in patients who are not adequately responsive to other forms of therapy, but only when diagnosis has been established as by biopsy and/or dermatologic consultation	No efficacy data in USPI	<ul style="list-style-type: none"> <li>• Risk of infection</li> <li>• Lymphoma</li> <li>• Tumor lysis syndrome in patients with rapidly growing tumors</li> <li>• Organ toxicity (liver, bone marrow, lung, kidney, GI)</li> <li>• Diarrhea &amp; ulcerative stomatitis</li> <li>• Severe skin reactions</li> <li>• Soft tissue necrosis &amp; osteonecrosis with concomitant radiotherapy</li> <li>• Teratogenicity (females and males)</li> <li>• Careful monitoring of dosing</li> <li>• Caution when used in older patients with diminished hepatic or renal function</li> </ul>
<b>Cyclosporine (prior to 1999)</b>	Adult non-immunocompromised patients with severe recalcitrant plaque psoriasis who have failed at least one systemic therapy or in patients for whom other systemic therapies are contraindicated or cannot be tolerated	PASI 75 response at Weeks 8-16: 51-79% (1.25 mg/kg BID)	<ul style="list-style-type: none"> <li>• Risk of infection</li> <li>• Malignancy</li> <li>• Hypertension</li> <li>• Kidney toxicity</li> <li>• Relapse upon cessation of therapy</li> <li>• Hepatotoxicity</li> <li>• Immunosuppression</li> <li>• Vaccination</li> <li>• Caution when used in older patients or patients with diminished renal function</li> <li>• Careful monitoring of patients</li> <li>• Monitoring of blood cyclosporine</li> </ul>

<b>Table 1      Summary of FDA-approved systemic therapies for the treatment of psoriasis</b>			
<b>Therapy (Year of Approval)</b>	<b>Indications</b>	<b>Efficacy (Dose Regimen used in Clinical Studies)</b>	<b>Safety/Tolerability (Warning and Precaution Section)</b>
<b>Acitretin (prior to 1999)</b>	Severe psoriasis in non-pregnant adults who are unresponsive to other therapies or whose clinical condition contra-indicates use of other treatments	Mean change in PGA at 8 weeks: –1.06 (25 mg daily) –0.06 (Placebo)  –1.57 to –2.00 (50 mg daily) –0.06 to –0.29 (Placebo)	<ul style="list-style-type: none"> <li>• Teratogenicity (females and males)</li> <li>• Hepatotoxicity</li> <li>• Bone abnormalities</li> <li>• Elevated lipids</li> <li>• Ophthalmologic effects including decreased night vision</li> <li>• Pancreatitis</li> <li>• Depression/psychiatric</li> <li>• Pseudotumor Cerebri</li> </ul>
<b>PUVA (prior to 1999)</b>	Severe recalcitrant, disabling psoriasis, not adequately responsive to other forms of therapy and when diagnosis is supported by biopsy	No efficacy data in USPI	<ul style="list-style-type: none"> <li>• Malignancy</li> <li>• Cataracts</li> <li>• Skin burning</li> <li>• Actinic degeneration</li> <li>• No sunbathing 24 hrs prior to and 48 hrs post PUVA</li> <li>• Wraparound sunglasses 24 hrs following methoxsalen ingestion</li> </ul>
<b>Efalizumab (2003)</b>	Adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy	PASI 75 Response at Week 12: 22-39% (1 mg/kg/wk) 2-5% (Placebo)	<ul style="list-style-type: none"> <li>• Risk of infection</li> <li>• Malignancies</li> <li>• Immune-mediated thrombocytopenia</li> <li>• Immune-mediated hemolytic anemia</li> <li>• Psoriasis worsening and variants</li> <li>• New onset/recurrence of psoriatic arthritis</li> <li>• Immunosuppression</li> <li>• Immunization</li> <li>• First dose reactions (headache, fever, nausea, vomiting)</li> </ul>
<b>Alefacept (2003)</b>	Adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy	PASI 75 Response at 2 weeks post dose: 21% (15 mg IM) 5% (Placebo)  14% (7.5 mg IV) 4% (Placebo)	<ul style="list-style-type: none"> <li>• Risk of infection</li> <li>• Malignancies</li> <li>• Lymphopenia</li> <li>• Immunosuppression</li> <li>• Allergic reactions</li> <li>• Hepatic injury</li> <li>• Monitoring CD4+ T lymphocyte levels</li> </ul>

<b>Table 1      Summary of FDA-approved systemic therapies for the treatment of psoriasis</b>			
<b>Therapy (Year of Approval)</b>	<b>Indications</b>	<b>Efficacy (Dose Regimen used in Clinical Studies)</b>	<b>Safety/Tolerability (Warning and Precaution Section)</b>
<b>Etanercept (2004)</b>	Adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy	PASI 75 Response at Week 12: 32% (25 mg BIW) 46-47% (50 mg BIW) 3-4% (Placebo)	<ul style="list-style-type: none"> <li>• Risk of infection</li> <li>• Malignancies</li> <li>• Hepatitis B reactivation</li> <li>• Neurologic events</li> <li>• Hematologic events</li> <li>• Allergic reactions</li> <li>• Latex sensitivity</li> <li>• Heart failure</li> <li>• Immunosuppression</li> <li>• Immunization</li> <li>• Autoimmunity</li> </ul>
<b>Infliximab (2006)</b>	Adult patients with chronic severe (ie, extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate	PASI 75 Response at Week 10: 70-72% (3 mg/kg) 75-88% (5 mg/kg) 2-6% (Placebo) at Weeks 0, 2, 6	<ul style="list-style-type: none"> <li>• Risk of infection</li> <li>• Malignancies</li> <li>• Hepatosplenic T-cell lymphoma</li> <li>• Heart failure (contraindication in NYHA Functional class III/IV)</li> <li>• Hepatitis B reactivation</li> <li>• Hepatotoxicity</li> <li>• Hematologic events</li> <li>• Hypersensitivity</li> <li>• Neurologic events</li> <li>• Autoimmunity</li> <li>• Immunization</li> </ul>
<b>Adalimumab (2008)</b>	Adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy and when other systemic therapies are medically less appropriate	PASI 75 Response at Week 16: 71-78% (40 mg EOW) 7-19% (Placebo)	<ul style="list-style-type: none"> <li>• Risk of infections</li> <li>• Malignancies</li> <li>• Hepatitis B reactivation</li> <li>• Hypersensitivity reactions</li> <li>• Neurologic events</li> <li>• Hematologic events</li> <li>• Heart failure</li> <li>• Immunosuppression</li> <li>• Immunization</li> <li>• Autoimmunity</li> </ul>
BID = twice daily; BIW = twice per week; EOW = every other week; GI = gastrointestinal; IM = intramuscular.			

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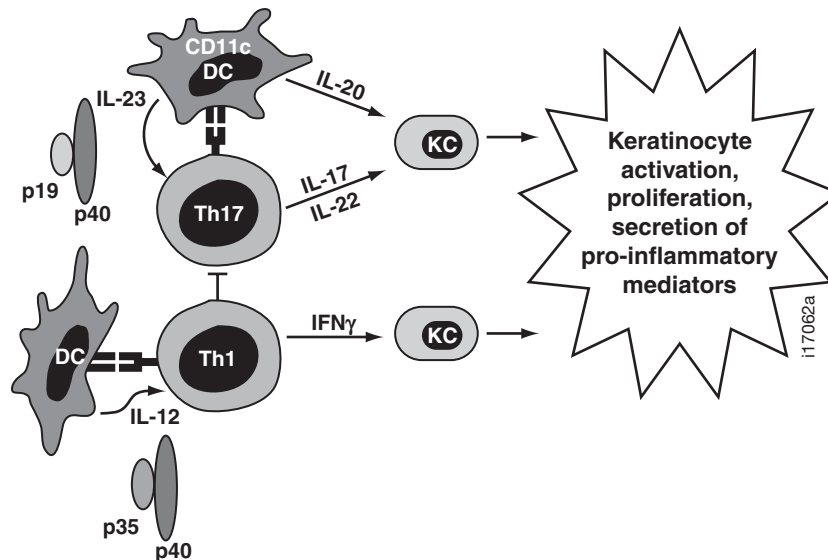
## 2.2 Psoriasis Pathophysiology

Aberrant immune responses have been linked to psoriasis pathogenesis, and cytokines or pathways that elicit these immune responses may represent appropriate therapeutic targets ([Nickoloff and Nestle, 2004](#)). Interleukins-12 and -23 (IL-12 and IL-23) are thought to play a significant role in the pathogenesis of psoriasis:

- Genetic polymorphisms in the genes that encode the shared p40 subunit of these cytokines, IL-12B, and one of the IL-23 receptor subunits, IL-23R, have been linked to psoriasis ([Cargill et al, 2007](#)). An uncommon IL-23R coding variant that confers protection against Crohn's disease ([Duerr et al, 2006](#)) has also been shown to confer protection against psoriasis ([Capon et al, 2007](#)).
- Gene and protein expression levels of IL-12, interferon gamma (IFN $\gamma$ ), and IL-23 are elevated in serum and skin lesions of psoriasis patients ([Torti and Feldman, 2007](#); [Roussaki-Schulze et al, 2005](#); [Arican et al, 2005](#); [Chan et al, 2006](#); [Piskin et al, 2006](#)).
- Targeting IL-12/23p40 in a mouse model of psoriasis ([Hong et al, 1999](#)) and in a humanized model using skin from human psoriasis donors transplanted onto immunodeficient mice (data on file, Centocor) suggest that antibodies to IL-12/23p40 may offer a therapeutic approach to treat psoriasis.

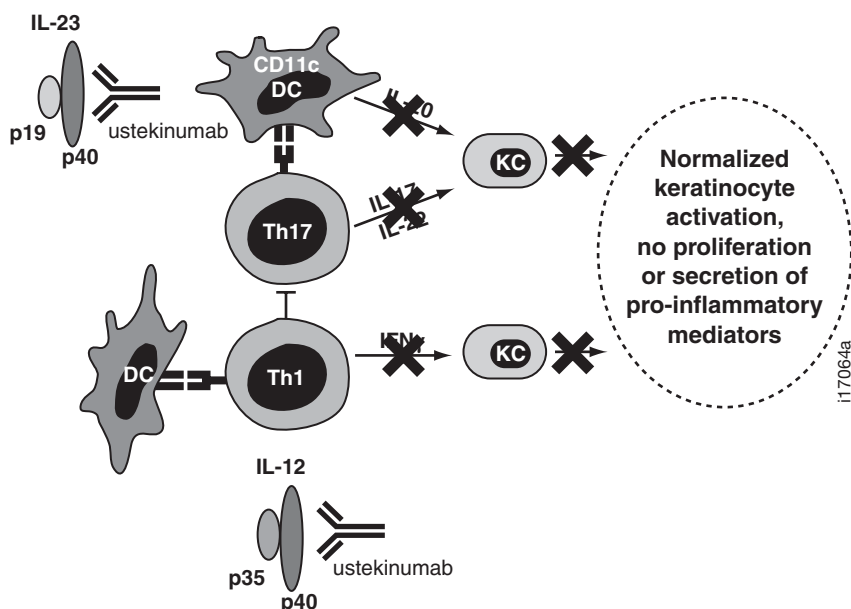
IL-12 and IL-23 are heterodimeric cytokines that are secreted by antigen presenting cells, including dendritic cells in the skin. They share a common p40 subunit that is covalently linked to a unique p35 (IL-12) or p19 (IL-23) subunit. IL-12 and IL-23 participate in immune function through natural killer (NK) cell activation and CD4<sup>+</sup> T cell differentiation towards the T helper (Th) 1 phenotype in response to IL-12 and a Th17 phenotype in response to IL-23.

Th1 and Th17 cells contribute to psoriasis pathophysiology by secreting IFN $\gamma$ , IL-17, and IL-22 that, in turn, activate keratinocytes (KC) to trigger keratinocyte proliferation, activation, and secretion of additional pro-inflammatory mediators. This cascade can lead to psoriasis skin pathology. The production of IL-12 and IL-23 and their downstream impact on Th1 and Th17 activation, as well as keratinocyte activation and psoriasis skin pathology are pictured in Figure 1 (modified from [Zaba et al, 2007](#)).



**Figure 1** Activated dendritic cells (DC) secrete IL-23 (p19p40) and IL-12 (p35p40), which results in Th17 and Th1 cell differentiation and activation. Th1 and Th17 cytokines induce KC activation, proliferation, and secretion of pro-inflammatory mediators that contribute to psoriasis skin pathology.

IL-12- or IL-23-mediated activation of Th1 and Th17 lymphocytes, as noted by secretion of IFN $\gamma$ , IL-17, and IL-22, can be inhibited by IL-12/23p40 blockade. This can prevent activation of KC and result in normalized skin pathology. A model for the impact of IL-12 and IL-23 neutralization on psoriasis immunopathology is shown in Figure 2 (modified from [Zaba et al, 2007](#)).



**Figure 2** Ustekinumab binds to IL-12/23p40 and prevents IL-12 and IL-23 from activating Th1 and Th17 cells, thus inhibiting the pathway leading to KC activation proliferation, and secretion of pro-inflammatory mediators, resulting in normalization of skin pathology.

Ustekinumab was tested in a humanized mouse model of psoriasis in which non-lesional skin from human psoriasis donors was transplanted onto immunodeficient mice. After acceptance of the grafts, the psoriatic process was triggered by the intradermal injection of autologous human activated T cells. Ustekinumab treatment prevented epidermal thickening and keratinocyte proliferation in this model. Collectively, these data suggest that IL-12/23p40 is an important disease target in psoriasis and that ustekinumab may offer an appropriate therapeutic approach to treat psoriasis pathogenesis.

### 3 Proposed Labeling

#### 3.1 Indication

The proposed indication for ustekinumab is:

Ustekinumab is indicated for the treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.



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## 3.2 Dosage and Administration

The proposed dosing recommendations for ustekinumab are as follows:

- Ustekinumab is administered by subcutaneous (SC) injection
  - For patients weighing  $\leq 100$  kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by dosing every 12 weeks.
  - For patients weighing  $> 100$  kg, the recommended dose is 90 mg initially and 4 weeks later, followed by dosing every 12 weeks.

In patients weighing  $> 100$  kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these patients

## 4 Background Information

### 4.1 Description of Molecule

Ustekinumab is a fully human IgG1 monoclonal antibody (mAb) of approximate molecular weight of 148,600 Daltons and is composed of 2 identical heavy chains and 2 identical kappa ( $\kappa$ ) light chains in a disulfide-linked heterodimeric structure. Ustekinumab binds with high affinity and specificity to the 40 kDalton protein subunit of IL-12 and IL-23. This subunit is called IL-12/23p40 and is the molecular target of ustekinumab.

### 4.2 Scientific Rationale and Mechanism of Action

#### 4.2.1 Role of IL-12 and IL-23 in Immune Response

In normal immune responses, IL-12 induced Th1 cells favor cell-mediated immunity and delayed type hypersensitivity, and are characterized by robust production of the proinflammatory cytokine IFN $\gamma$  ([Trinchieri, 2003](#)). Whereas, IL-23, IL-6, and IL-1 $\beta$  work in combination to promote the differentiation, expansion, and survival of human Th17 cells that produce IL-17A, IL-17F, and IL-22, which are cytokines known to stimulate many inflammatory responses ([Ouyang et al, 2008](#)).

- In mice, Th1 and Th17 cells contribute to protective immune responses to viral, bacterial, intracellular protozoa, and fungal pathogens ([Bowman et al, 2006](#); [Torti and Feldman, 2007](#)). These observations are primarily reported in genetically deficient, ie, “knock-out” mice or upon very high doses of neutralizing antibody administration.
- Nonclinical models with mice genetically deficient in IL-12 and/or IL-23 suggest that IL-12 may play a protective role in tumor immunity ([Colombo and Trinchieri,](#)

2002; Airoidi et al, 2007) whereas, IL-23 may promote tumor incidence and growth (Langowski et al, 2006). In addition, pharmacologic doses of both IL-12 and IL-23 have also been shown to suppress tumor growth in mouse models (Hu et al, 2006; Kaiga et al, 2007; Brunda et al, 1993; Smyth et al, 2000).

- In contrast to observations in experimental mouse systems, only modest antitumor activity was noted for human clinical trials of pharmacologic doses of IL-12 and severe dose-limiting toxicities including patient deaths were observed (Leonard et al, 1997; Portielje et al, 1999). The role of endogenous IL-12 in human tumor biology remains poorly understood, and elevated levels may be a marker of poor prognosis (Chun et al, 2008). Thus, for IL-12 and perhaps IL-23, it is difficult to correlate observations in mouse systems to human responses.
- Humans who have been identified as genetically deficient for genes IL-12/23p40 or the receptor IL-12R $\beta$ 1, (as well as other genes within the Th1 and Th17 cascades, such as IFN $\gamma$  receptor 1 and 2, STAT1 (signal transducers and activators of transcription), and nuclear factor-kB essential modulator [NEMO]) are susceptible to recurring *Salmonella* species and nontuberculous (non-TB) primary *Mycobacteria* infection, including bacille Calmette-Guérin (BCG). However, they appear to have normal resistance to ubiquitous viruses and fungi, gram-positive and other gram-negative bacteria, and common opportunistic protozoa (Novelli and Casanova, 2004; Fieschi and Casanova, 2003; Filipe-Santos et al, 2006). A malignancy or cardiovascular risk has not been reported in this patient population, though the numbers of patients identified is small (approximately 220) and most were reported to be in the first four decades of life (Filipe-Santos et al, 2006; and Fieschi and Casanova 2003).

#### 4.2.2 Role of IL-12 and IL-23 in Immune-mediated Disease

Inflammation mediated by IL-12 and IL-23 may also play a role in certain immune-mediated inflammatory diseases.

- IL-12 and IL-23 have been shown to mediate several experimental mouse models of immune-mediated disease, such as psoriasis, Crohn's disease, multiple sclerosis (MS), rheumatoid arthritis, Type I diabetes mellitus, neuritis, thyroiditis, and uveitis. (Kopp et al, 2003; Chan et al, 2006; Hong, 1999; Tozawa et al, 2003; Chen et al, 2006; Bao et al, 2002; Zacccone et al, 1999; Murphy et al, 2003; Fujihira et al, 2000; Tarrant et al, 1998).
- IL-12 and IL-23 expression is increased in human immune-mediated diseases, including psoriasis (Torti and Feldman, 2007), MS (McFarland and Martin, 2007), and Crohn's disease (Pizarro and Cominelli, 2007). In addition, IL-12/23p40 targeted treatment in humans suppresses psoriasis and Crohn's disease (Krueger et al, 2007; Mannon et al, 2004).

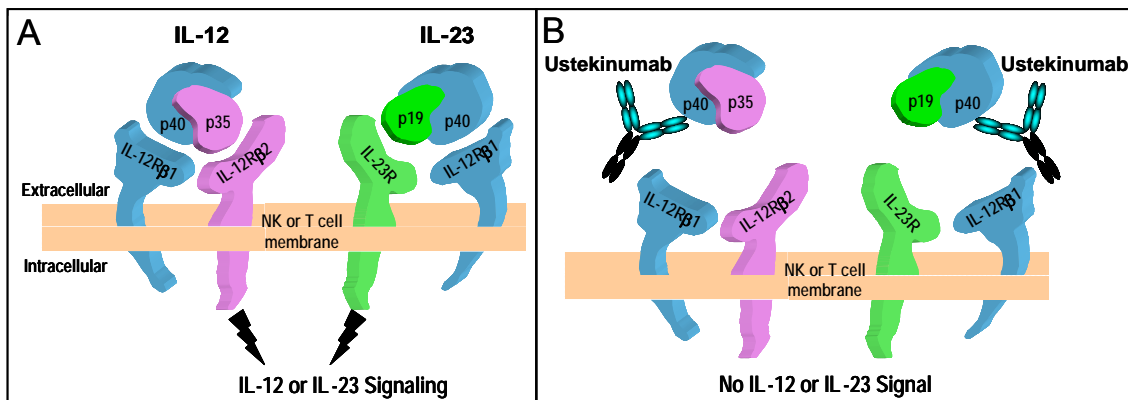
- While there are limited data on the role of IL-23 in cardiovascular disease ([Cheng et al, 2008](#)), ample nonclinical data suggest that IL-12 is involved in atherosclerosis. IL-12 protein and IFN $\gamma$  gene expression can be detected in human atherosclerosis plaques ([Uyemura et al, 1996](#)), human serum of patients with acute myocardial infarction (MI; [Zhou et al, 2001](#)) and unstable angina ([Fernandes et al, 2004](#)), and in early stages of mouse atherosclerosis ([Lee et al, 1999](#)). Mouse models suggest that IL-12 may accelerate atherosclerosis ([Lee et al, 1999](#)), and that inhibition of IL-12 in these models attenuates atherosclerosis ([Hauer et al, 2005](#)). In aggregate these results suggest that interruption of IL-12 should be beneficial in atherosclerosis.

### 4.2.3 Mechanism of Action of Ustekinumab

IL-12 and IL-23 are secreted cytokines and do not exist as transmembrane proteins. The IL-12p35 and IL-23p19 subunits are covalently linked to IL-12/23p40 intracellularly and the protein complexes are secreted as functional heterodimeric cytokines. In mouse systems, the p40 subunit has been reported to exist in both monomeric and homodimeric secreted forms. Evidence for mouse p40 homodimers with bioactivities independent of IL-12 and IL-23 have been reported ([Cooper and Khader, 2007](#)). However, the existence of human p40 homodimers is limited to a single unconfirmed report in asthmatic bronchoalveolar lavage ([Walter et al, 2001](#)) and can only be demonstrated in vitro in cell lines transgenically transfected with the p40 gene. Human p40 homodimers are not detectable in normal IL-12 producing human monocytes ([Carra et al, 2000](#)). Therefore, the relevance of mouse p40 homodimer observations to human biology is unclear. Thus to date, IL-12 and IL-23 are the only bioactive human cytokines described to contain IL-12/23p40.

IL-12 and IL-23 mediate cellular activity through binding to 2-chain receptor complexes expressed on the surface of CD4<sup>+</sup> T cells or NK cells. As illustrated in Figure 3A, the IL-12R $\beta$ 1 receptor chain binds to the common p40 subunit of IL-12 and IL-23, providing the primary binding interaction between IL-12 and IL-23 and their receptor complexes. The partner subunits, namely IL-12p35 and IL-23p19, trigger specific intracellular signaling through binding to IL-12R $\beta$ 2 ([Presky et al, 1996](#)) or IL-23R ([Parham et al, 2002](#)), respectively.

The molecular mechanism of action of ustekinumab is shown in Figure 3B. Ustekinumab binds to the shared p40 protein subunit of human IL-12 and IL-23 and inhibits IL-12 and IL-23 bioactivity by preventing their interaction with their cell surface IL-12R $\beta$ 1 receptor protein. Through this mechanism of action, ustekinumab effectively neutralizes IL-12 and IL-23-mediated cellular responses.



**Figure 3 Illustration of IL-12 and IL-23 and their receptor complexes and the mechanism of action of ustekinumab**

(A) Heterodimeric cytokines IL-12 (p35 + p40) and IL-23 (p19 + p40) are shown binding to their 2-chain receptor complexes expressed on the surface of NK or T cells. The IL-12 receptor complex is comprised of IL-12Rβ1 partnered with the signaling chain IL-12Rβ2. The IL-23 receptor complex is composed of IL-12Rβ1 partnered with the signaling chain IL-23R. (B) Ustekinumab is shown with Fab fragments in blue highlighting and Fc fragments in solid black. Ustekinumab binds to the shared p40 subunit of human IL-12 and IL-23 and prevents IL-12Rβ1 binding and subsequent intracellular signaling of the partner receptor chains.

#### 4.2.4 Cellular Pharmacology

In target binding characterization studies, ustekinumab was shown to bind to the p40 protein subunit of human IL-12 and IL-23 with high affinity, specificity, and the expected 2:1 ligand to antibody ratio. The molecular interactions between ustekinumab and IL-12 and IL-23 were determined through crystal structure and protein mutagenesis analysis and are well understood.

Ustekinumab should not bind to cell surfaces since IL-12 and IL-23 only exist as secreted proteins. Furthermore, ustekinumab did not bind to IL-12 or IL-23 that was already bound to cell surface receptor complexes. Thus, there is no evidence that antibody Fc-mediated effector functions that result in cellular depletion, such as antibody dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity, contribute to the mechanism of action of ustekinumab. Rather, the molecular mechanism of action of ustekinumab is mediated through binding to the shared p40 subunit of human IL-12 and IL-23 and preventing ligation to the IL-12Rβ1 receptor chain.

Through this mechanism of action, ustekinumab neutralized the following IL-12 (Th1)-mediated in vitro cellular responses:

- Intracellular phosphorylation of STAT 4 and STAT 6;
- Cell surface expression of CD95 (Fas), cutaneous lymphocyte antigen (CLA), and IL-12R $\beta$ 2;
- NK and lymphokine activated killer cell (LAK) lytic activity;
- IFN $\gamma$  cytokine production.

Ustekinumab also neutralized the following IL-23 (Th17)-mediated in vitro cellular responses:

- Intracellular STAT3 phosphorylation;
- Production of IL-17A, IL-22, IL-17F, and IL-10.

Thus, ustekinumab effectively neutralized all IL-12 (Th1)- and IL-23 (Th17)-mediated cellular responses tested using in vitro bioassays. It is important to note that immune pathways often have multiple points of origin, allowing for compensatory mechanisms to achieve host protection. Ustekinumab will effectively neutralize IL-12- and IL-23-immune responses, but will not impact these responses if stimulated through other cytokine or cellular activities.

### **4.3 Nonclinical Safety (Toxicology and Toxicokinetics)**

#### **4.3.1 Tissue Crossreactivity and Nonclinical Species Selection**

In two independent immunohistochemical tissue cross-reactivity studies on a range of human tissues, no binding of ustekinumab to normal human tissues was observed. Ustekinumab binds and neutralizes human and nonhuman primate IL-12 and IL-23, but does not bind to IL-12 or IL-23 from mouse, rat, or dog. In addition, in vivo pharmacological activity of ustekinumab was demonstrated in a nonhuman primate disease model of experimental autoimmune encephalomyelitis ([Brok et al 2002](#), ['t Hart et al, 2005](#)). The cynomolgus monkey was selected as a relevant species for nonclinical pharmacology, pharmacokinetics, and toxicology evaluation. In vitro studies showed that ustekinumab neutralized IL-12 from humans and cynomolgus monkeys with similar concentration dependence.

#### **4.3.2 General Toxicity**

In multiple dose toxicity studies in cynomolgus monkeys, ustekinumab was generally well-tolerated following IV doses up to 45 mg/kg/week for up to 1 month and following twice-weekly subcutaneous (SC) doses up to 45 mg/kg for 6 months.

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- No ustekinumab-related mortality, moribundity or adverse effects on body weight, food consumption, body temperature, ophthalmoscopic or hematology parameters were observed. No ustekinumab-related changes in serum chemistries were observed, including total cholesterol and triglyceride levels.
  - One high dose (45 mg/kg) monkey in the 6-month toxicity study, showed clinical signs that were associated with bacterial enteritis.
  - No ustekinumab-related effects on heart rate, blood pressure, respiratory rate, or electrocardiograms were observed.
  - Postmortem, there were no ustekinumab-related macroscopic observations or adverse effects on organ weights at necropsy, and no ustekinumab-related histopathology findings. There were no tumors or pre-neoplastic changes observed in histopathology evaluations in any toxicity study in cynomolgus monkeys following ustekinumab treatments.
  - Because ustekinumab does not bind to rodent IL-12 or IL-23, rodents are not pharmacologically relevant species and carcinogenicity studies with ustekinumab were not conducted.

### 4.3.3 Immunotoxicity Evaluations

Because ustekinumab binds two cytokines (IL-12 and IL-23) that contribute to NK and T cell differentiation and activation, immunotoxicity evaluations were performed in cynomolgus monkeys. Furthermore, IL-12 can antagonize immune responses mediated through "Th2" T cell lineages that may contribute to allergy and asthma immunopathologies ([Mosmann and Coffman, 1989](#)). Thus, it was theoretically possible that IL-12 neutralization via ustekinumab could exacerbate Th2-mediated diseases such as asthma.

In the ustekinumab immunotoxicity evaluations, the following observations were made:

- No adverse effects of ustekinumab on functional immune response to a neoantigen (KLH); delayed type hypersensitivity responses (tetanus toxin) or ex vivo lymphoproliferative responses to T cell mitogens.
- No adverse effects on lymphoid organ weights.
- No ustekinumab-related histopathological alterations in lymphoid tissues of juvenile, young adult or adult monkeys.

- 
- No depletion or alterations in circulating lymphocyte subpopulations and no changes in the distribution of T- and B-lymphocytes in lymphoid tissue.
  - No exacerbation of asthmatic responses (eosinophilia in bronchoalveolar lavage, bronchoconstriction) was observed in *Ascaris summ* sensitized monkeys.

#### 4.3.3.1 Developmental and Reproductive Toxicity Studies

Ustekinumab was well tolerated in Developmental and Reproductive Toxicity (DART) studies conducted in cynomolgus monkeys at dosages up to 45 mg/kg which included:

- A male fertility study;
- An embryofetal development (EFD) toxicity study (both intravenously and subcutaneously administered ustekinumab);
- A combined EFD and Pre- and Postnatal Development Toxicity Study.

No ustekinumab-related developmental toxicity, teratogenicity, or reproductive toxicity was revealed in these studies.

#### 4.3.4 Toxicokinetics

Toxicokinetic evaluations indicated that the pharmacokinetic properties of ustekinumab in monkeys are predictable:

- Dose proportional increases in exposure and maximum concentration of drug (C<sub>max</sub>) were observed and the volume of distribution was approximately equal to the intravascular space.
- Following SC administration of ustekinumab to cynomolgus monkeys high levels of exposure were achieved.
- Mean half-life values following twice weekly SC dosing were between 12 to 22 days.
- Antibodies to ustekinumab were not detected in toxicology study monkeys administered ustekinumab.

The No Observed Adverse Effect Level for ustekinumab in general, developmental and reproductive toxicity studies was 45 mg/kg. Based on recommended dosing, psoriasis patients are projected to receive < 1.0 mg/kg, thus the high dose in toxicology studies is approximately 45-fold higher than the highest proposed dose for psoriasis patients.

In Table 2, the C<sub>max</sub> values following administration of the last 45 mg/kg dose of ustekinumab in toxicity studies are shown in relation to the median C<sub>max</sub> (20.3 µg/mL)

observed in psoriasis subjects following 4 weekly 90 mg SC injections of ustekinumab in study T04. The average C<sub>max</sub> values observed following repeated-dosing in toxicity studies were approximately 105 to 186 times higher than the observed median C<sub>max</sub> in psoriasis subjects following 4 weekly 90 mg SC injections (the highest exposure studied in Phase 2).

<b>Table 2 Relationship between observed C<sub>max</sub> values in toxicity studies and observed serum concentrations in psoriasis subjects following ustekinumab dosing</b>			
<b>Study Description and/or duration</b>	<b>Study No.</b>	<b>Observed C<sub>max</sub> (µg/mL) in monkeys following the last 45 mg/kg dose</b>	<b>Ratio: C<sub>max</sub> in tox study/median C<sub>max</sub> observed following 4 weekly 90 mg SC injections (T04)</b>
1 month pilot IV study	T-099-003	2138	105
1-month GLP IV Study	T-099-004	3628	179
Embryofetal Development/ ~1 month	T-2001-001	2950	145
<b>Developmental and Reproductive Toxicology</b>			
Local Tolerance	T-2001-003	2460	121
Chronic/ 6 months	T-2001-004	2347	116
Male Fertility/ 13-weeks	T-2005-015	3782	186
Embryofetal Development/ ~1 month	T-2002-005	2344	116
Combined Embryofetal Development/Pre and Postnatal Development/ ~5-6 months (Dams)	T-2004-009	3048	150

In the 6-month chronic toxicity study, monkeys in the high dose group were subcutaneously administered ustekinumab twice-weekly for 26 weeks at 45 mg/kg. The cumulative dose administered to these cynomolgus monkeys in this study was 2340 mg/kg ustekinumab (52 x 45 mg/kg doses of ustekinumab). Based on recommended dosing, psoriasis patients are projected to receive dosing at < 1.0 mg/kg per administration, and the frequency of proposed administration is every 12 weeks. Based on these assumptions, a patient who received ustekinumab for 55 years would receive no more than a cumulative dose of 237 mg/kg (4.3 doses/year x 55 years x 1 mg/kg/dose), approximately 10-fold lower than administered to monkeys in the chronic toxicity study.



### **4.3.5 Nonclinical Safety Summary**

- Data from the toxicology program, primarily conducted in nonhuman primates, suggest that ustekinumab has a broad therapeutic window.
- An adequate safety profile has been demonstrated in multiple dose toxicity studies in nonhuman primates extending up to 26 weeks in duration with exposures up to 45 mg/kg, administered either weekly by the IV route of administration or twice weekly by the SC route.
- No adverse effects of ustekinumab were observed in an acute asthma model or in safety pharmacology (cardiac, respiratory or central nervous system) and immunotoxicity evaluations in toxicology studies. No preneoplastic changes or ustekinumab-related findings were observed in histopathology evaluations.
- No ustekinumab-related maternal toxicity, teratogenicity or birth defects were observed in developmental toxicity evaluations and fertility parameters were not impacted by treatment with anti-IL12/23 antibodies
- The No Observed Adverse Effect Level in toxicity studies (45 mg/kg) was approximately 45-fold higher than the highest dose (< 1 mg/kg) proposed for psoriasis patients.

## **4.4 Clinical Pharmacology**

The primary focus of the clinical pharmacology program for ustekinumab was to evaluate the pharmacokinetics, pharmacodynamics, and immunogenicity in subjects with moderate to severe plaque psoriasis, the condition for which a treatment indication is sought (see Table 3). In addition, ustekinumab was also investigated in subjects with MS, Crohn's disease, and PsA, and in healthy subjects. Overall, the pharmacokinetics of ustekinumab were consistent across the different study populations.

**Table 3 Listing of ustekinumab psoriasis studies evaluating clinical pharmacology**

Study number	Study phase	Dose groups and route of administration	Number of ustekinumab-treated subjects evaluated for PK	Sampling scheme <sup>a</sup>
T01	1	0.09 to 4.5 mg/kg single dose IV	18	Intensive
T02	1	0.27 to 2.7 mg/kg single dose SC	17	Intensive
T04	2	45 and 90 mg single/multiple dose SC	94	Intensive
T08	3	45 and 90 mg multiple dose SC	753	Sparse
T09	3	45 and 90 mg multiple dose SC	1212	Sparse

<sup>a</sup> Intensive sampling schemes enable determination of the full PK profile using a non-model-based approach (eg, noncompartmental analysis). Sparse sampling schemes require a model-based approach to characterize the full PK profile.

#### 4.4.1 Absorption

- In subjects with psoriasis, ustekinumab was slowly absorbed after a single SC administration and reached the maximum serum concentration in approximately 7 to 14 days.
- The maximum serum concentration and area under the serum concentration-versus-time curve (AUC) values increased in an approximately dose-proportional manner after a single IV dose ranging from 0.09 mg/kg to 4.5 mg/kg (approximately 8 mg to 405 mg) or after a single SC dose ranging from approximately 24 mg to 240 mg based on an median weight of 90 kg in subjects with psoriasis.
- The bioavailability of ustekinumab was estimated to be 57.2% following a single SC administration.

#### 4.4.2 Distribution

- The median volume of distribution values ranged from approximately 57 mL/kg to 83 mL/kg following a single IV administration in subjects with psoriasis.

#### 4.4.3 Metabolism and Elimination

- As a fully human IgG1κ mAb, ustekinumab is expected to be metabolized in the same manner as any endogenous immunoglobulin gamma (IgG; degraded into small peptides and amino acids via catabolic pathways), and is subject to similar elimination.
- The median half-life for ustekinumab is approximately 3 weeks, similar to a typical half-life for an endogenous IgG.

- The half-life values were generally consistent across all studies in subjects with psoriasis, MS, Crohn's disease, and healthy subjects. Ustekinumab half-life values were also consistent between different routes of administration and between fixed and weight-adjusted doses.
- The median systemic clearance values following a single IV administration ranged from 1.8 mL/day/kg to 2.3 mL/day/kg in subjects with psoriasis.

#### **4.4.4 Impact of Food on the Absorption**

Food is not expected to have any impact on the absorption of ustekinumab because it is administered subcutaneously.

#### **4.4.5 Population Pharmacokinetics**

Population pharmacokinetic (PK) analysis of ustekinumab was performed using a one-compartment model in subjects with psoriasis from the two Phase 3 studies to identify and quantify factors that could contribute to the variability in the systemic exposure of ustekinumab. Of the demographic factors (eg, gender, race, age, body size), baseline subject physical or biochemical characteristics, medical history, or concomitant medications, only subject weight, comorbidity of diabetes, and positive immune response status to ustekinumab were found to affect the systemic exposure to ustekinumab by at least 20% in subjects with moderate to severe plaque psoriasis. Diabetes and immune response were not associated with an impact on efficacy necessitating any adjustment of the proposed dosing. However, further analysis suggested efficacy was impacted by subject weight (see Section 5.3.3.9.1), which was a clinically relevant factor in determining the proposed dosing regimen.

#### **4.4.6 Potential for Drug Interactions**

No formal drug-drug interaction studies were conducted with ustekinumab. As a fully human IgG1 $\kappa$  mAb, ustekinumab possesses no or very low propensity for drug-drug interaction ([Seitz and Zhou, 2007](#)).

Potential drug-drug interactions were evaluated using a population pharmacokinetic approach among the 28 most frequently used concomitant medications (including atorvastatin, metformin, acetylsalicylic acid, ibuprofen, and paracetamol) in the Phase 3 studies. None of the concomitant medications had a significant effect upon the apparent clearance of ustekinumab. No immunosuppressants were allowed to be used concomitantly in either study.

#### **4.4.7 Immunogenicity**

The incidence of antibodies to ustekinumab was low and similar across all psoriasis studies despite differences in doses, schedules and routes of administration, formulations, and study intervals.

The overall incidence of antibodies to ustekinumab in the combined Phase 3 psoriasis studies was 3.7%. Antibody titers in the Phase 3 studies were generally low with the majority (66.2%) being  $\leq 1:80$ . Titer did not differ across doses, and the incidence of antibodies to ustekinumab did not appear to increase over time. As the rate of positive antibodies was low, the overall effect of antibodies on efficacy was limited (see Section 5.3.3.10) and there was no apparent relationship between antibodies to ustekinumab and injection site reactions (see Section 7.2.1.6.2). Note that the presence of ustekinumab in serum may interfere with detectability of antibodies to ustekinumab. However, the incidence of antibodies to ustekinumab did not increase in subjects who became drug free after withdrawal from ustekinumab therapy.

#### **4.4.8 Pharmacodynamics**

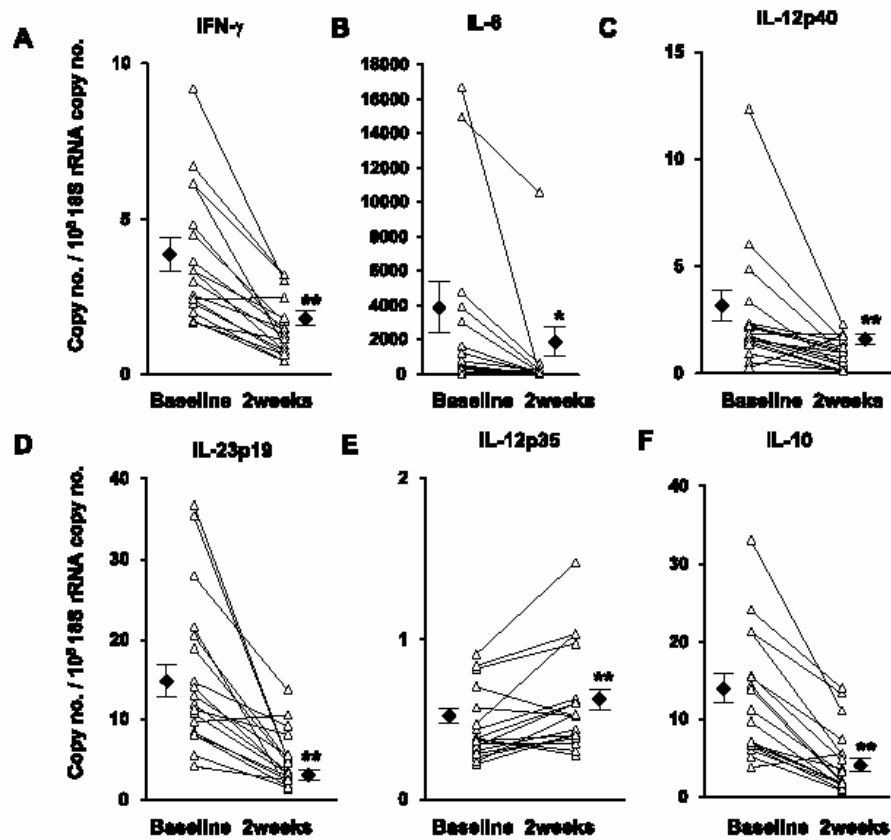
A direct pharmacodynamic assay of the activity of ustekinumab has not been identified. The systemic and local effects of ustekinumab have been assessed to better understand the molecular pathways impacted by ustekinumab treatment.

##### **4.4.8.1 Systemic Analyses**

IL-12/23p40 is the molecular target of ustekinumab and can be detected in baseline serum samples of subjects with psoriasis. Upon ustekinumab treatment, levels of IL-12/23p40 appear to increase in serum by enzyme-linked immunosorbent assay (ELISA). This is presumed to be ustekinumab-bound IL-12/23p40, though an assay that distinguishes bound versus unbound IL-12/23p40 has not been developed. Likewise, quantitative assays for bioactive IL-12 (p35 + p40) or IL-23 (p19 + p40) are not currently available. In the Phase 1 and Phase 2 studies, lymphocyte subset analyses showed that ustekinumab did not impact the absolute number of circulating white blood cells, which differs from some marketed biologic therapies for psoriasis. In addition, the proportion of naïve (CD45RA) or memory T cells (CD45RO) was not altered in these studies. Interestingly, there was a decrease in the number of CLA positive T cells, a subset of T cells thought to traffic to the skin in psoriasis patients and contribute to psoriasis pathogenesis ([Sigmundsdottir et al, 2001](#)). IL-12 can induce CLA expression and ustekinumab will neutralize IL-12-mediated CLA expression in vitro ([Reddy et al, 2007](#)). Additional assessments were completed to measure changes in peripheral blood cell activation states (CD69, CD25, HLA-DR) and selected serum protein levels (IFN $\gamma$ , IL-5, IL-8, IL-10, CCL27, tumor necrosis factor alpha [TNF- $\alpha$ , ICAM-1) but no significant impact by ustekinumab was demonstrated. Thus, a peripheral pharmacodynamic marker was not identified for ustekinumab activity.

#### **4.4.8.2 Skin Analyses**

To assess skin pathology post ustekinumab treatment, biopsies were collected in the Phase 1 and 2 studies and predicted responses were seen both histologically and via gene expression analysis in lesional skin of subjects treated with ustekinumab. Consistent with the observed clinical benefit, ustekinumab had a significant impact on epidermal thickness returning the epidermis to a thickness approaching that of normal non-lesional skin. A dose effect was shown in the Phase 2 study where a single dose of 45 mg by 12 weeks showed a trend of decreasing thickness but was not significant where as a 90 mg single dose or multiple doses (weekly x 4) at 45 mg or 90 mg showed significant reductions at 12 weeks post-treatment. A decrease in the degree of T cell infiltration and cellular proliferation was also observed following ustekinumab treatment. Lesional skin gene expression was assessed in a Phase 1 study. IL-12/23p40, IL-23p19, IFN- $\gamma$  and other related genes were assessed at baseline and 2 weeks following treatment with ustekinumab. Figure 4 shows that IL-12/23p40, IL-23p19, IFN- $\gamma$ , IL-5, and IL-8 are significantly decreased following 2 weeks of treatment with ustekinumab. The gene changes are compatible with the histological changes and support the mechanism of action of ustekinumab in psoriasis (see Section 4.2.3).



**Figure 4 Lesional skin cytokine mRNA expression before and after ustekinumab treatment**

RNA was prepared from the one-half of punch biopsies obtained from the psoriatic skin lesions at baseline and 2 weeks after ustekinumab administration. Quantitative reverse transcriptase polymerase chain reaction (RTPCR) was performed for the indicated genes. Gene expression levels were normalized to 18S rRNA. The expression levels of each cytokine for all the subjects ( $n = 18$ ) at baseline and 2 weeks posttreatment are presented. The mean  $\pm$  SE of all subjects is indicated by the diamond symbol ( $\diamond$ ). \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; statistically significant differences between baseline and 2 weeks posttreatment. (Figure from [Toichi et al, 2006](#)).

#### 4.4.9 Immunology and Immunocompetence

Lymphocyte subset analysis and T cell functionality of peripheral blood mononuclear cells (PBMCs) from subjects with psoriasis following 12 weeks of ustekinumab treatment showed the following:

- No alteration in the proportion of naïve (CD45RA) or memory (CD45RO) T lymphocytes
- No alteration in the proportion of CD69, CD25 (early activation markers) or HLA-DR (a late activation marker).
- No effect on the ability of PBMCs ex vivo to respond to mitogenic stimuli as assessed by IFN $\gamma$  and IL-5 release.

These data show no observed depletion or expansion of any measured subsets of T cells. These ex vivo assessments required washing of the cells which removed ustekinumab and as such are not reflective of the functionality of the cells in the presence of drug but do suggest that any potential impact of ustekinumab on these functions are reversed when drug is removed or cleared.

In Phase 1 studies, subjects were tested for the effect of ustekinumab on response to polyvalent pneumococcal antigen vaccine (non-memory antibody response) and tetanus toxoid (antigen recall response; see Table 4). These were single dose studies and the numbers of subjects tested were limited however no dose-related effects of ustekinumab on these responses were observed.

<b>Table 4      Effect of ustekinumab on response to polyvalent pneumococcal vaccine (non-memory antibody response) and tetanus toxoid (antigen recall response)</b>			
<b>Study</b>	<b>Route of Admin. Single Dose (Range of Doses)</b>	<b>Subjects with Positive Antibody Response to Pneumococcal Vaccine of Total (%)</b>	<b>Subjects with Positive Antibody Response To Tetanus Toxoid of Total (%)</b>
Phase 1 Psoriasis	IV (0.09 - 4.5 mg/kg)	Ustekinumab 13 of 18 (72.2%)	Not tested
Phase 1 Psoriasis	SC (0.27 - 2.7 mg/kg)	Placebo 2 of 4 (50%) Ustekinumab 10 of 13 (76.9%)	Placebo 1 of 2 (50%) Ustekinumab 5 of 7 (71.4%)
Phase 1 Multiple Sclerosis	SC (0.27 - 2.7 mg/kg)	Placebo 2 of 4 (50%) Ustekinumab 11 of 15 (73.3%)	Placebo 3 of 3 (100%) Ustekinumab 7 of 13 (53.8%)

#### **4.4.10 Clinical Pharmacology Summary**

##### **Pharmacokinetics**

- Ustekinumab was slowly absorbed after a single SC administration and reached the maximum serum concentration in approximately 7 to 14 days.
- The bioavailability of ustekinumab was estimated to be 57.2% following a single SC administration.
- The median half-life for ustekinumab is approximately 3 weeks, similar to a typical half-life for an endogenous IgG.
- Based on the population pharmacokinetic covariate analyses, in conjunction with impact on clinical efficacy, subject weight was found to be the most clinically relevant factor in determining the dose regimen.

##### **Immunogenicity**

- The overall incidence of antibodies to ustekinumab in the combined Phase 3 psoriasis studies was 3.7%. Antibody titers were generally low with the majority (66.2%) being  $\leq 1:80$ .

##### **Pharmacodynamics**

- Ustekinumab had no impact on the numbers of circulating lymphocyte populations or selected serum protein levels.
- Biopsies performed in Phase 1 and 2 studies demonstrated histological and gene expression changes in lesional skin that support the mechanism of action of ustekinumab in psoriasis.

##### **Immunology and Immunocompetence**

- There was no depletion or expansion in naïve, memory, or activated T cell subsets by ustekinumab.
- There was no effect on the ability of PBMCs ex vivo to respond to mitogenic stimuli as assessed by IFN $\gamma$  and IL-5 release.
- In Phase 1 studies, ustekinumab did not impact non-memory antibody response or antigen recall response.



## **5 Clinical Development Program**

### **5.1 Clinical Studies**

The psoriasis clinical development program of ustekinumab consisted of 3 well controlled Phase 2 (T04) and Phase 3 (T08 and T09) clinical studies in 2316 subjects with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy. Additionally, 2 Phase 1 studies were completed and these studies suggested that ustekinumab has efficacy in psoriasis even with a single IV or SC dose (Table 5). The efficacy demonstrated in the completed Phase 2 study (T04) formed the basis of dose selection for the pivotal studies, T08 and T09. These 3 studies will be the focus of the efficacy review.

T08 and T09 are ongoing, 5-year studies to evaluate the long-term safety and efficacy of ustekinumab.

**Table 5 Ustekinumab clinical studies in subjects with psoriasis submitted in the BLA**

<b>Study Total follow-up (Follow-up during placebo-control period) Total Subjects</b>	<b>Severity of Plaque Psoriasis</b>	<b>Treatment Group (# of subjects)</b>
<b>PHASE 1</b>		
T01 16 weeks (none) Total Subjects = 18	BSA involvement $\geq 3\%$	Weight adjusted doses: - 0.09 mg/kg single IV dose (n = 4) - 0.27 mg/kg single IV dose (n = 4) - 0.9 mg/kg single IV dose (n = 5) - 4.5 mg/kg single IV dose (n = 5)
T02 24 weeks (24 weeks) Total Randomized Subjects = 21	BSA involvement $\geq 3\%$	Weight adjusted doses: - Placebo (n = 4) - 0.27 mg/kg single SC dose (n = 5) - 0.675 mg/kg single SC dose (n = 4) - 1.35 mg/kg single SC dose (n = 4) - 2.7 mg/kg single SC dose (n = 4)
<b>PHASE 2</b>		
T04 52 weeks (20 weeks) Total Randomized Subjects = 320	PASI $\geq 12$ ; BSA involvement $\geq 10\%$	Fixed doses: - Placebo (n = 64) - Placebo $\rightarrow$ 90 mg single SC dose (n = 47) <sup>a</sup> - 45 mg single SC dose (n = 64) - 90 mg single SC dose (n = 64) - 45 mg weekly x 4 SC doses (n = 64) - 90 mg weekly x 4 SC doses (n = 64)  See Figure 5 for additional study design details.
<b>PHASE 3 (ongoing 5-year studies)</b>		
T08 $\geq 52$ weeks <sup>b</sup> (12 weeks) Total Randomized Subjects = 766	PASI $\geq 12$ ; BSA involvement $\geq 10\%$	Fixed doses: - Placebo (n = 255) - Placebo $\rightarrow$ 45 mg regimen <sup>c</sup> (n = 123) - Placebo $\rightarrow$ 90 mg regimen <sup>c</sup> (n = 120) - 45 mg SC Weeks 0, 4 then q12w (n = 255) - 90 mg SC Weeks 0, 4 then q12w (n = 256)  See Figure 8 for additional study design details.
T09 28 weeks (12 weeks) Total Randomized Subjects = 1230	PASI $\geq 12$ ; BSA involvement $\geq 10\%$	Fixed doses: - Placebo (n = 410) - Placebo $\rightarrow$ 45 mg regimen <sup>c</sup> (n = 197) - Placebo $\rightarrow$ 90 mg regimen <sup>c</sup> (n = 195) - 45 mg SC Weeks 0, 4 then q12w (n = 409) - 90 mg SC Weeks 0, 4 then q12w (n = 411)  See Figure 9 for additional study design details.
<sup>a</sup> At Week 20, subjects in the placebo group received a single dose of 90 mg.		
<sup>b</sup> Includes all data available through the date the last subject completed the Week 52 visit (ie, through the data cutoff for the BLA).		
<sup>c</sup> The placebo groups crossed over to receive 45 mg or 90 mg at Weeks 12 and 16 then q12w.		

### **5.1.1 Study Population in Phase 2 and Phase 3**

Adults with moderate to severe plaque psoriasis (defined as  $\geq 10\%$  of total body surface area (BSA) and a Psoriasis Area and Severity Index (PASI) score of  $\geq 12$  who were candidates for phototherapy or systemic therapy) were enrolled in the Phase 2 and Phase 3 studies to evaluate the monotherapy treatment with ustekinumab. This study population was consistent with the study populations evaluated in clinical studies of other biologics ([Ellis and Krueger, 2001](#); [Leonardi et al, 2003](#); [Reich et al, 2005](#); [Menter et al, 2007](#)).

### **5.1.2 Major Study Objectives in Phase 2 and Phase 3**

The Phase 2 and Phase 3 studies combined evaluated:

- The safety and efficacy of ustekinumab versus placebo in treating subjects with moderate to severe plaque psoriasis.
- The safety and efficacy of long-term continuous use of ustekinumab.
- The impact of ustekinumab on quality of life.
- The safety and efficacy of retreatment with ustekinumab after a treatment-free interval.

### **5.1.3 Efficacy Outcome Measures in Phase 2 and Phase 3**

A comprehensive evaluation of both physician- and patient-reported outcomes was included in the Phase 2 and Phase 3 studies.

#### **5.1.3.1 Physician Reported Outcomes**

Efficacy was measured using the PASI, which quantifies the extent of psoriasis and the degree of plaque erythema, scaling and thickness on the 4 body areas: head, trunk, upper limbs, and lower limb (see [Appendix A](#)). Possible scores range from 0 (no disease) to 72 (maximal disease). The following measures of treatment success are commonly employed:

- 50% improvement in PASI from baseline (PASI 50): Minimally acceptable criteria for treatment success ([Gordon et al, 2005](#)).
- 75% improvement in PASI from baseline (PASI 75): Standard measure for preferred level of response.
- 90% improvement in PASI from baseline (PASI 90): Standard measure for high level of response, consistent with a Physician's Global Assessment (PGA) of clear or almost clear.

Efficacy was independently substantiated by 1 of 2 PGA Scales:

- A relative PGA was employed in Phase 2 (see [Appendix B](#)). This PGA documents the physician's assessment of the subject's psoriasis status. The PGA is assessed relative to baseline condition with scores ranging from clear (1) to worse (6). Clear (1) or excellent (2) was identified as the preferred response.
- A static PGA was employed in the Phase 3 studies (see [Appendix C](#)). This PGA evaluated overall lesions graded for induration, erythema, and scaling with a final score ranging from clear (0) to severe (5). Clear (0) or almost clear (1) was identified as the preferred response.

Nail psoriasis was evaluated in Phase 3 using the Nail Psoriasis Severity Index (NAPSI). The NAPSI is an index used for assessing and grading the severity of nail psoriasis, a characteristic of psoriasis that is difficult to treat and often adversely impacts physical and mental functioning and well-being ([de Berker, 2000](#); [Farber and Nall, 1992](#); [de Jong et al, 1996](#)).

### **5.1.3.2 Patient-reported Outcomes**

Patient-reported outcomes including both disease-specific and general outcomes were assessed in the Phase 2 and Phase 3 clinical study program.

#### **5.1.3.2.1 Disease Specific Patient-reported Outcomes**

Two skin disease-specific patient-reported outcome instruments were used in Phase 3:

- The Dermatology Life Quality Index (DLQI) is a skin disease-specific instrument designed to assess the impact of the disease on a subject's quality of life ([Finlay and Khan, 1994](#)). It is a 10-item questionnaire that assesses 6 different aspects of quality of life: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. Possible DLQI scores range from 0 to 30. A DLQI of 0 indicates no detectable impairment on patients' quality of life.
- The Itch Visual Analog Scale (VAS) was used to evaluate skin pruritus with scores ranging from 0 (no itch at all) to 10 (severe itch).

#### **5.1.3.2.2 General Patient-reported Outcomes**

Four separate general patient-reported outcome instruments were used in the combined Phase 2 and Phase 3 program:

- The 36-item short form health survey (SF-36) was used to evaluate subjects' overall quality of life ([Ware and Sherbourne, 1992](#)). The SF-36 contains 36 questions which capture both mental health and physical functioning in the Mental Component Summary and Physical Component Summary scores. Scores range from 0 to 100 with higher scores indicating better quality of life.
- The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire that measures anxiety and depression. The HADS contains 2 scales, including the HADS-A for anxiety and the HADS-D for depression, which each contain 7 items. Each scale has a range of 0 - 21, with lower scores indicating better quality of life (eg, no anxiety or depression). The HADS has established reliability ([Zigmond and Snaith, 1983](#)) and validity ([Moorey et al, 1991](#)).
- The Work Limitations Questionnaire (WLQ) is a 25-item questionnaire designed to measure the degree to which employed individuals are experiencing limitations on-the-job due to their health problems. The WLQ has 4 scales for measuring work limitations, including physical demands, time management demands, mental-interpersonal demands, and output demands. For each of the scales, scores range from 0 (limited none of the time) to 100 (limited all of the time). Studies have supported the validity and reliability of the WLQ in various patient populations ([Lerner et al, 2001](#); [Lerner et al, 2002](#); [Walker et al, 2005](#)).
- Productivity was assessed using a Visual Analog Scale (VAS) with scores ranging from 0 to 10, with lower scores indicating greater productivity.

## 5.2 Phase 2 Study

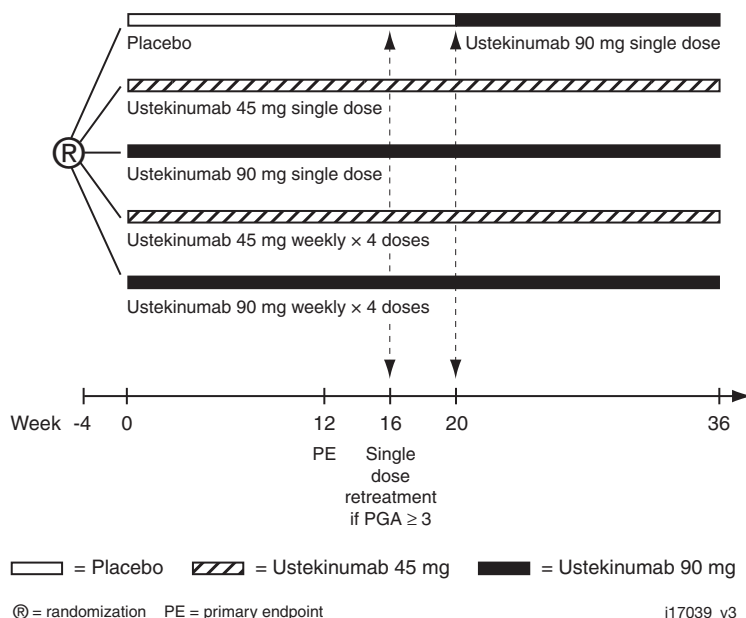
### 5.2.1 Study Design

The Phase 2 placebo-controlled, double-blind, parallel-group, study compared the safety and efficacy of placebo to 4 exposure levels of subcutaneously administered ustekinumab:

- A single 45 mg dose
- A single 90 mg dose
- 4 weekly 45 mg doses (180 mg total)
- 4 weekly 90 mg doses (360 mg total)

Subjects were randomized in equal proportions to the treatment groups, and the randomization was stratified by investigational site and weight relative to 95 kg. At Week 16, subjects with a PGA less than excellent ( $\geq 3$ ) received 1 additional injection of their originally randomized dose. At Week 20, placebo-randomized subjects crossed over to receive 1 x 90 mg injection of the ustekinumab (see Figure 5 for study design schematic).

The range of exposures studied in Phase 2 was selected based on the efficacy results of T01, T02, and PK/PD modeling. The range of doses was intended to achieve AUC exposures and C<sub>max</sub> that would further characterize the dose-concentration-response relationship in efficacy. Potential retreatment at Week 16 was based on Phase 1 data that showed the duration of response was approximately 12 to 16 weeks. This allowed evaluation of the safety and efficacy of retreatment.

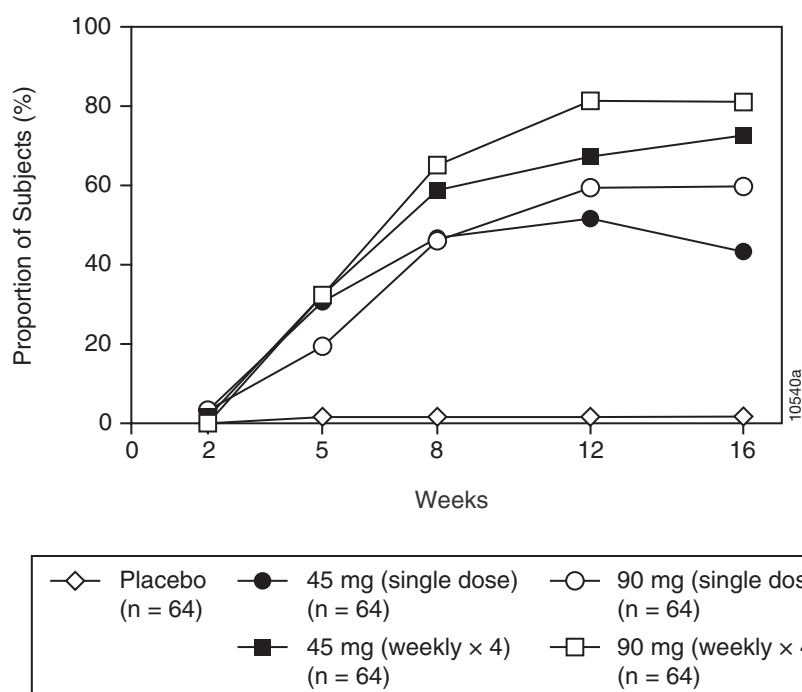


**Figure 5 Study design overview for T04**

## 5.2.2 Biologic Activity

### Dose response and high level of efficacy observed over range of exposures studied

A high proportion of subjects treated with ustekinumab met the primary endpoint (PASI 75 response at Week 12), and clear evidence of a dose response in efficacy was observed. A total of 51.6%, 59.4%, 67.2%, and 81.3% of subjects treated with sequentially higher exposures of ustekinumab (45 mg single dose, 90 mg single dose, 4 weekly 45 mg doses, and 4 weekly 90 mg doses, respectively) achieved PASI 75 response at Week 12 compared with 1 subject (1.6%) receiving placebo ( $p < 0.001$  for each ustekinumab group vs placebo; see Figure 6).



**Figure 6** Proportion of subjects achieving PASI 75 response through Week 16 by visit; subjects randomized at Week 0 in T04

The high level of efficacy and the dose response in efficacy were independently confirmed by other PASI or PGA response thresholds. At Week 12, the following was observed:

- A PASI 90 response at Week 12 was achieved by 23.4%, 29.7%, 43.8%, and 51.6% of subjects treated with ustekinumab 45 mg single dose, 90 mg single dose, 4 weekly 45 mg doses, and 4 weekly 90 mg doses, respectively, compared with 1 subject (1.6%) receiving placebo ( $p < 0.001$  for each group compared with placebo).
- A PGA of clear or excellent at Week 12 was achieved by 50.8%, 53.1%, 71.9%, and 82.8% of subjects treated with ustekinumab 45 mg single dose, 90 mg single dose, 4 weekly 45 mg doses, and 4 weekly 90 mg doses, respectively, compared with 0% of subjects receiving placebo ( $p < 0.001$  for each group compared with placebo).
- PASI 75 responses were generally consistent across subgroups defined by baseline demographic features, clinical disease characteristics, and psoriasis medication history.

*Duration of response*

- In general, peak response was estimated to occur approximately 12 weeks after dosing, but in some subjects, occurred as soon as 8 weeks postdose. PASI 75 response rates generally began to decline after peak response was achieved.
- Results suggested that maintaining PASI 75 response would require maintenance therapy with dosing intervals of q8w to q12w since loss of response was observed with longer intervals (ie, 16 weeks after dosing).

*Impact of weight on efficacy*

A greater proportion of subjects weighing  $\leq 95$  kg achieved a PASI 75 response, compared with subjects weighing  $> 95$  kg, especially in the single dose groups, suggesting that clinical response may be affected by weight.

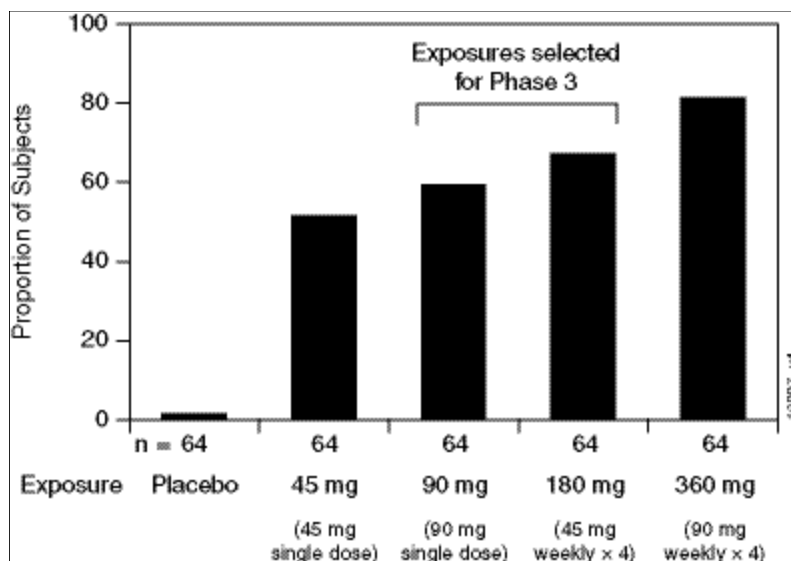
*Efficacy of retreatment*

Subjects with a PGA score  $\geq 3$  at Week 16 were retreated with a single administration of ustekinumab at their originally randomized dose. With retreatment, the proportion of subjects achieving PASI 75 response was similar to or higher than the proportion of subjects in this subset who originally achieved a PASI 75 response.

### **5.2.3 Rationale for Dose Selection in Phase 3**

Dosing selected for initial exposures (ie, exposure through 12 weeks of therapy) corresponded to the middle exposures studied in Phase 2 (ie, 90 mg and 180 mg), which were projected to achieve exposures at the mid- to upper-level of the dose-response curve of efficacy (see Figure 7), but below the plateau of dose-response.





**Figure 7** Proportion of subjects achieving a PASI 75 response at Week 12; subjects randomized at Week 0 in T04

Continuous maintenance dosing was selected for study since psoriasis is a chronic disease, and subjects in Phase 2 experienced a return of disease after discontinuation of therapy. The frequency of dosing in Phase 3 was based on the time to peak response and the time to loss of response following initial dosing in Phase 2. In general, peak response was estimated to occur approximately 12 weeks after dosing, but in some subjects, occurred as soon as 8 weeks postdose. PASI 75 response rates generally began to decline after peak response was achieved. A q12w maintenance regimen was chosen as a conservative estimate of the frequency of dosing that would be required to consistently maintain response in a high proportion of patients. This dosing frequency was also projected to maintain low, but detectable serum concentrations of ustekinumab in most subjects, thereby potentially reducing immunogenicity.

To achieve generally stable levels of exposure over time rather than a high initial peak of exposure, the initial exposures (ie, 90 mg and 180 mg) were divided into two doses spread 4 weeks apart (ie, 45 mg or 90 mg at Weeks 0 and 4) prior to initiating q12w maintenance dosing.

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## 5.3 Phase 3 Studies

T08 and T09 are the pivotal studies that confirm the efficacy and safety of ustekinumab and are identical in design through Week 28. Data submitted in the BLA included:

- All data through the date the last subject completed the Week 52 visit in T08 (ie, 52 weeks of data in the last subject enrolled in the study, but up to 68 weeks of data in the first subject enrolled). Note, approximately 65% of subjects have data at Week 56.
- All data through Week 28 in T09.

Both studies are currently ongoing and will continue for 5 years to evaluate the long-term efficacy and safety of ustekinumab.

### **T08**

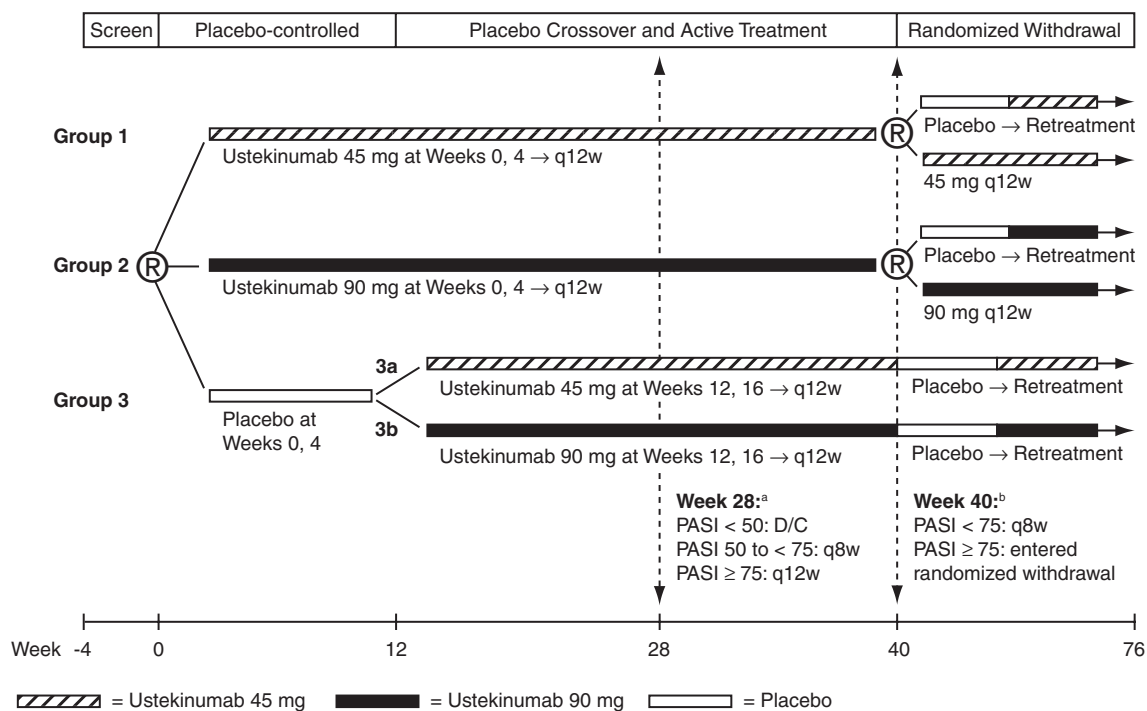
T08 initially evaluated safety and efficacy of ustekinumab versus placebo in 766 subjects with moderate to severe plaque psoriasis and the efficacy of maintenance therapy q12w dosing for subjects who were PASI 75 responders (see Figure 8 for study design schematic).

***Placebo-controlled Period:*** Subjects randomized to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4. Subjects randomized to placebo received placebo at Weeks 0 and 4.

***Placebo Crossover and Active Treatment Period:*** Subjects randomized to ustekinumab began q12w dosing starting at Week 16. Subjects originally randomized to placebo crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16 followed by q12w dosing.

***Maintenance Dosing/Randomized Withdrawal Period:*** To evaluate the therapeutic benefit of maintenance dosing with ustekinumab, all subjects originally randomized to ustekinumab who were PASI 75 responders at Weeks 28 and 40 were re-randomized to either maintenance dosing of ustekinumab q12w or to placebo (ie, withdrawal of therapy). Subjects who were re-randomized to placebo at Week 40 reinitiated ustekinumab at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at Week 40.

Note that subjects who were partial responders at Week 28 (subjects who achieved  $\geq 50\%$  but less than 75% improvement in PASI from baseline) or who were PASI 75 nonresponders at Week 40 (subjects with  $< 75\%$  improvement in PASI from baseline) escaped and underwent dosing interval adjustment to q8w dosing. Observational data on these subjects is provided.



D/C = discontinued; PASI = Psoriasis Area and Severity Index; ® = randomization; q8w = every 8 weeks; q12w = every 12 weeks

<sup>a</sup> At Week 28, in all groups, nonresponders (PASI < 50) discontinued study agent, partial responders (PASI 50 to < 75) began q8w dosing, and PASI responders (PASI ≥ 75) received q12w dosing.

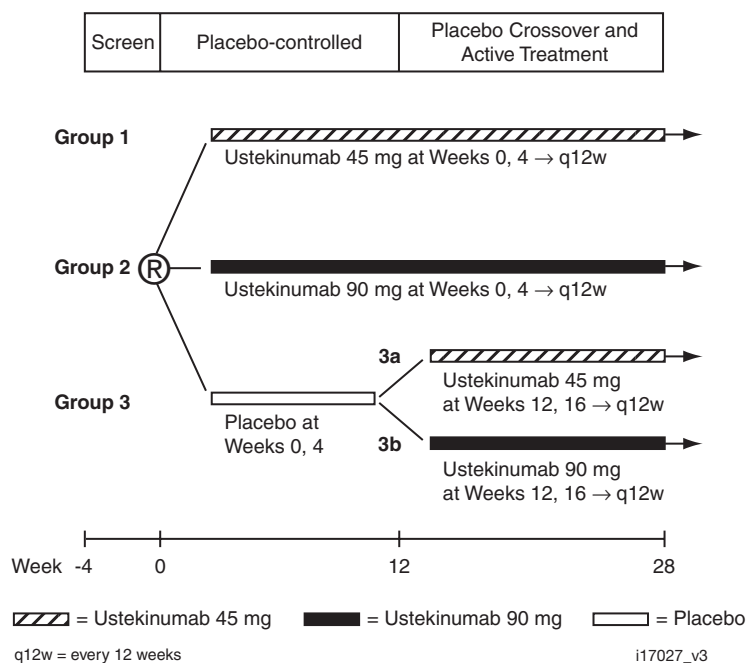
<sup>b</sup> At Week 40, PASI responders to q12w dosing in Groups 1 and 2 were randomized to either placebo or continued q12w ustekinumab (at their original dose), while those in Group 3 received placebo. At loss of therapeutic effect, subjects receiving placebo began retreatment at their dosing regimen prior to withdrawal. In all groups, nonresponders or partial responders (PASI < 75) were adjusted to q8wk dosing. Subjects receiving q8w dosing continued q8w dosing.

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**Figure 8 Study design overview for T08 through Week 76**

## **T09**

T09 initially evaluated safety and efficacy of ustekinumab versus placebo in 1230 subjects with moderate to severe plaque psoriasis (Figure 9).



**Figure 9 Study design overview for T09 through Week 28**

**Placebo-controlled Period:** Subjects randomized to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4. Subjects randomized to placebo received placebo at Weeks 0 and 4.

**Placebo Crossover and Active Treatment Period:** Subjects randomized to ustekinumab began q12w dosing starting at Week 16. Subjects originally randomized to placebo crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16 followed by q12w dosing.

Randomized dosing interval adjustment was evaluated in T09 after Week 28. These data will be submitted at a later date.

### 5.3.1 Study Population

T08 enrolled 766 subjects and T09 enrolled 1230 subjects (see Table 6 for baseline demographics and baseline disease characteristics). In both studies, the randomization of subjects to treatment was stratified based on investigational site, weight ( $\leq 90$  kg or  $> 90$  kg based on a median weight of approximately 90 kg in T04), and previous experience with conventional systemic therapies (inadequate response to, intolerance to, or contraindication to  $< 3$  or  $\geq 3$  conventional systemic therapies including cyclosporine, MTX, acitretin, and PUVA). Stratification by previous experience with conventional systemic therapies was in agreement with European regulatory needs, and was intended to ensure treatment allocation balance in a potentially more resistant population.

Baseline demographics and disease characteristics were generally consistent across the 2 studies and were balanced across the placebo and both ustekinumab treatment groups within each study. A predominance of male subjects participated, as has been observed in clinical studies of other biologics (Leonardi et al, 2003; Lebwohl et al, 2003a; Lebwohl et al, 2003b; Menter et al, 2008). The majority of subjects were Caucasian (> 90%), consistent with psoriasis prevalence reported among different racial groups (Stern et al, 2004; Gelfand et al, 2005). Baseline disease characteristics indicated a population of subjects with moderate to severe plaque psoriasis that were generally consistent with disease characteristics in subject enrolled in studies of other biologics (Ellis and Krueger, 2001; Leonardi et al, 2003; Menter et al, 2007; Gordon et al, 2006; Menter et al, 2008). More than 50% of subjects had previously used at least 1 systemic agent and more than 50% were previously treated with phototherapy. In addition, at least one-third of subjects had previously used of a biologic. Subjects showed impairment in quality of life at baseline.

**Table 6 Baseline demographic and disease characteristics in Phase 3**

	T08	T09
Subjects randomized	766	1230
Sex: Male	69.3%	68.3%
Race: Caucasian	93.6%	91.7%
Median age (years)	45.5	47.0
Median weight (kg)	91.60	88.60
Geographic region		
Europe	1.7%	17.5%
Canada	48.4%	48.7%
US	49.9%	33.8%
Median BSA%	21.0%	20.0%
BSA $\geq$ 20%	55.0%	53.8%
Median PASI score (0-72)	17.60	17.50
PASI $\geq$ 20	33.9%	35.2%
PGA score of severe or marked ( $\geq$ 4)	43.8%	39.7%
Median psoriasis disease duration (years)	18.33	18.53
Median age at diagnosis (years)	23.0	24.0
History of PsA	33.7%	24.8%
Median DLQI (0-30)	10.0	12.0
DLQI $\geq$ 10	54.1%	59.1%

**Table 6 Baseline demographic and disease characteristics in Phase 3**

	T08	T09
Previous treatment with conventional systemics		
≥ 1 systemic agents	55.4%	55.9%
≥ 2 systemic agents	26.5%	25.8%
≥ 3 systemic agents	9.3%	9.7%
Previous use of biologics	51.2%	37.9%
Previous use of phototherapy	64.2%	67.4%
Inadequate response to, were intolerant to, or had a contraindication to		
≥ 1 conventional systemic agents	53.4%	60.5%
≥ 2 conventional systemic agents	27.9%	35.5%
≥ 3 conventional systemic agents	11.0%	16.3%

### 5.3.2 Study Endpoints

#### Primary endpoint

The primary efficacy endpoint in both T08 and T09 was the proportion of subjects with a PASI 75 response (referred to as PASI 75 responders) at Week 12.

#### Major secondary endpoints

The major secondary endpoints in both T08 and T09 were:

- The proportion of subjects with a PGA score of cleared (0) or minimal (1) at Week 12.
- The change in DLQI from baseline at Week 12.

A major secondary endpoint only in T08 evaluated:

- Maintenance of response over time in subjects randomized to placebo or continued q12w dosing at Week 40 based on the time to loss of PASI 75 response. Subjects who continued on q12w dosing (45 mg q12w and 90 mg q12w combined) were compared with subjects who received placebo.

*Other Analyses*

- Efficacy over time was evaluated with PASI, PGA, and DLQI in both T08 and T09.
- T08 also evaluated:
  - Quality of life assessed by the SF-36.
  - Nail psoriasis assessed by NAPS1.
  - Pruritus evaluated by the Itch VAS.
  - Productivity assessed by the Productivity VAS.
- T09 also evaluated:
  - Anxiety and depression using the HADS.
  - Impact on work limitations using the WLQ.
  - Productivity assessed by the Productivity VAS.

**5.3.3 Efficacy**

Table 7 summarizes the initial efficacy through Week 28 observed in T08 and T09 (assessed by key efficacy endpoints with primary endpoint and PGA major secondary endpoint shown in bold). Week 28 is displayed because it represents the final efficacy assessment in the T09 study, and it represents efficacy at trough steady state drug levels.

**Table 7 Key psoriasis endpoints in Phase 3**

	T08 Ustekinumab			T09 Ustekinumab		
	Placebo <sup>a</sup>	45 mg	90 mg	Placebo <sup>a</sup>	45 mg	90 mg
Subjects randomized	255	255	256	410	409	411
PASI 50 response <sup>f</sup>						
Week 12 <sup>b</sup>	10.2%	83.5%	85.9%	10.0%	83.6%	89.3%
Week 28	NA	91.2%	96.3%	NA	92.9%	95.0%
PASI 75 response <sup>f</sup>						
<b>Week 12<sup>b,c</sup></b>	<b>3.1%</b>	<b>67.1%</b>	<b>66.4%</b>	<b>3.7%</b>	<b>66.7%</b>	<b>75.7%</b>
Week 28	NA	71.2%	78.6%	NA	69.5%	78.5%
PASI 90 response <sup>f</sup>						
Week 12 <sup>b</sup>	2.0%	41.6%	36.7%	0.7%	42.3%	50.9%
Week 28	NA	49.2%	55.6%	NA	44.8%	54.3%
PGA of Cleared/Minimal <sup>f</sup>						
<b>Week 12<sup>b,d</sup></b>	<b>3.9%</b>	<b>60.4%</b>	<b>61.7%</b>	<b>4.9%</b>	<b>68.0%</b>	<b>73.5%</b>
Week 28	NA	58.8%	66.3%	NA	61.2%	70.0%
Median percent improvement in NAPSI						
Week 12 <sup>b</sup>	0.0	25.0	25.0	NA	NA	NA
Week 24 <sup>e</sup>	NA	50.0	50.0	NA	NA	NA

NA = Not Available.

<sup>a</sup> The placebo group crossed over to 45 mg or 90 mg at Week 12; therefore, data for the placebo group are not available after Week 12.<sup>b</sup>  $p \leq 0.001$  for each ustekinumab group versus placebo.<sup>c</sup> Primary endpoint (shown in bold).<sup>d</sup> Major secondary endpoint (shown in bold).<sup>e</sup> Week 28 timepoint not collected.<sup>f</sup> An intention-to-treat analysis was employed for Week 12 analyses but not for Week 28. However, < 4% of subjects were not included in the analyses due to missing data at Week 28 across the 2 studies.

### 5.3.3.1 Efficacy Through Week 12

In Phase 3, initial regimens of 45 or 90 mg at Week 0 and 4 led to a statistically significant, rapid onset of efficacy.

- By Week 4, significantly greater proportions of subjects in the 45 mg and 90 mg groups achieved a PASI 75 response compared with placebo.
- High proportions (66.4% to 75.7% across ustekinumab groups in each study) of subjects achieved a PASI 75 response at Week 12 (the primary endpoint), consistent with results from Phase 2.



- 
- Comparable high levels of efficacy were observed using PGA as a measure of response.
  - Improvements in nail psoriasis (median percent improvement in NAPSI of 25.0 percentage points in both ustekinumab groups) were evident by Week 12.

### **5.3.3.2 Efficacy Through Week 28/40 (Placebo Crossover and Active Treatment Period)**

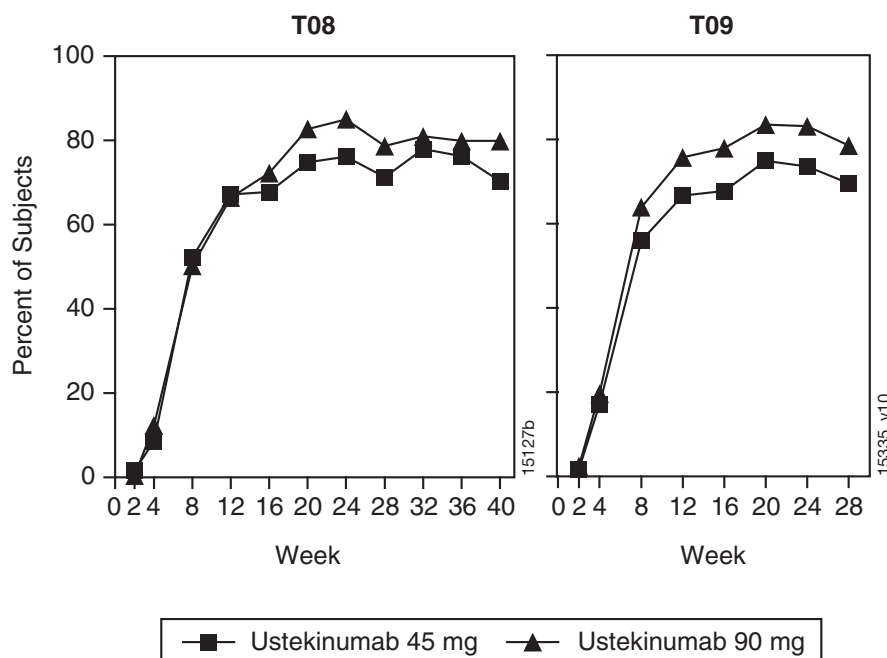
With maintenance dosing at Week 16, response rates across all PASI or PGA thresholds continued to improve beyond Week 12 in both T08 and T09.

- Maximum or near maximum responses in PASI and PGA were observed at Weeks 20 to 24 (see Figure 10 for PASI 75 response rates).
- At Week 28, over 90% of subjects were PASI 50 responders in both the 45 mg and 90 mg groups, at least 70% of subjects achieved a PASI 75 response, and approximately 50% of subjects achieved a PASI 90 response. The efficacy levels observed at Week 28 were remarkably similar between T08 and T09. In both studies, both the 45 mg and 90 mg regimens resulted in high levels of efficacy.
- With maintenance dosing at Weeks 16 and 28, response rates were generally maintained through Week 40.
- The placebo-crossover groups demonstrated generally similar PASI and PGA response rates after 16 weeks of ustekinumab treatment.
- Nail psoriasis continued to show improvements (median percent improvement in NAPSI of 50.0% in both ustekinumab groups) through Week 24.

### **5.3.3.3 Dose Response in Efficacy**

The proportion of subjects achieving a PASI 75 response was approximately 8 to 10 percentage points higher in subjects in the 90 mg group compared with subjects in the 45 mg group at the time of maximum or near maximum response (see Figure 10). The difference in response rates between the 45 mg and 90 mg groups generally persisted over time through Week 40 in T08.

Response rates were slightly higher 4 and 8 weeks after a dose than at the end of the dosing interval with modest “periodicity” of response (compare responses at Weeks 20 and 24 versus Week 28, respectively).



**Figure 10 Proportion of subjects achieving PASI 75 response over time; randomized subjects in Phase 3**

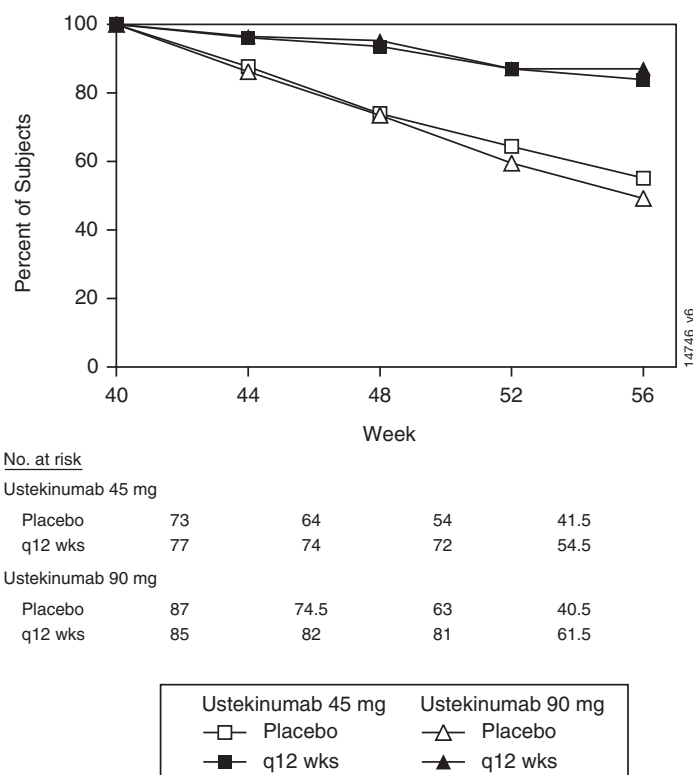
Additional observations on dose response:

- The dose response largely resulted from higher efficacy in subjects with weight > 100 kg who received 90 mg dosing (see Section 5.3.3.9.1).
- Similar patterns of dose-response were also observed when PGA was used as the measure of efficacy.
- Generally similar patterns of dose response were observed in the placebo crossover groups.

#### 5.3.3.4 Long-term Maintenance Efficacy/Randomized Withdrawal Period

To evaluate the benefit of long-term maintenance therapy, all subjects who were PASI 75 responders at both Weeks 28 and 40 were randomized at Week 40 to maintenance therapy or withdrawal of therapy. Week 40 was chosen to assure that maximum response was achieved by most subjects and that drug levels would have reached steady state. Survival analysis techniques using life-table estimates were used to analyze the major secondary endpoint, time to loss of PASI 75 response. In this analysis, once subjects lost response at any visit, they were considered nonresponders for all subsequent visits.

- Maintenance of PASI 75 response through at least 1 year was significantly superior in subjects receiving q12w maintenance therapy compared with subjects withdrawn from ustekinumab (87.0% of subjects on every 12 weeks maintenance therapy compared with 61.7% of subjects withdrawn from therapy,  $p < 0.001$ ; see Figure 11 for life table estimates in each of the individual treatment groups vs the respective withdrawal groups).

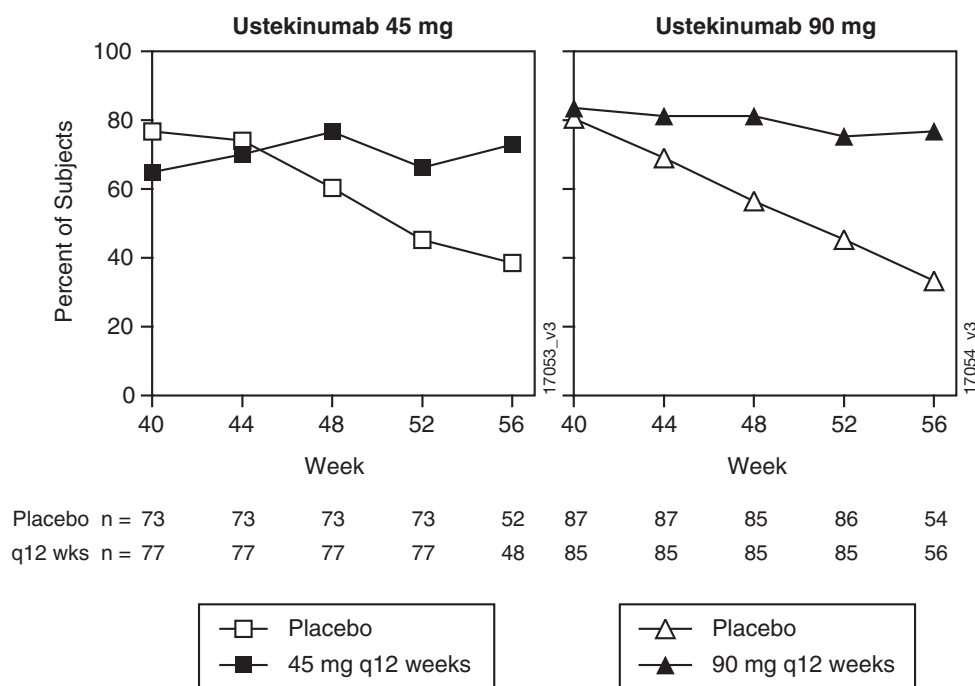


**Figure 11 Life-table estimates of the percent of subjects maintaining PASI 75 response; subjects randomized at Week 40 in T08**

- Subjects withdrawn from ustekinumab at Week 40 experienced re-emergence of psoriasis soon after therapy was interrupted. Separation in response rates emerged by Week 44 (4 weeks after a missed dose), when 96.3% of subjects in the combined maintenance therapy group maintained a PASI 75 response compared with 86.9% in the combined withdrawal group.
- This disparity in PASI 75 rates increased progressively over time and at the end of the first missed dosing interval (ie, at Week 52), the PASI 75 response rates were over 25 percentage points lower in subjects withdrawn from ustekinumab.

In addition to the survival analysis, the proportion of subjects who achieved PASI 50, PASI 75, and PASI 90 responses at each visit were analyzed. Similar patterns of response were observed.

While the PASI is an established tool for evaluating improvement and return of psoriasis in clinical studies, it is not routinely used in clinical practice (Louden et al, 2004). The PGA (a general assessment by the physician of scaling, erythema and elevation over the entire body) may be more easily used by physicians in clinical practice to make treatment decisions. The benefit of maintenance therapy is also observed when measured by PGA (see Figure 12). Note that not all subjects in the randomized withdrawal portion of the study had a Week 40 PGA of cleared (0) or minimal (1), demonstrating some discordance in efficacy as measure by PGA and PASI.

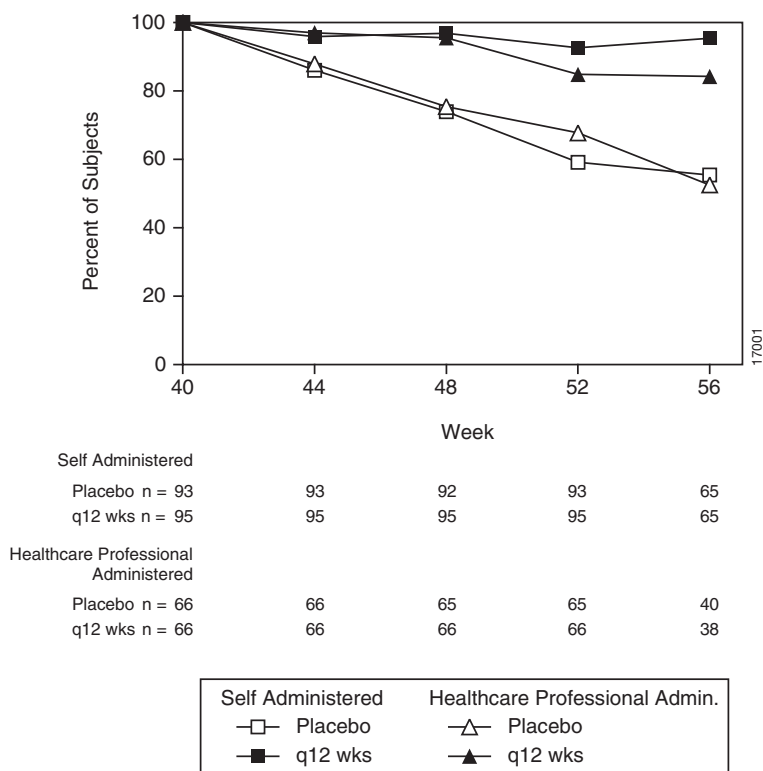


**Figure 12** Percent of subjects achieving a PGA of minimal or cleared from Week 40 through Week 56 by visit; subjects randomized at Week 40 in T08

Therefore, in subjects who responded to ustekinumab treatment over time (ie, PASI 75 responders at Weeks 28 and 40), psoriasis gradually returned after missing 1 ustekinumab dose. This observation was consistent over multiple efficacy measures. When psoriasis returns, 2 doses may be necessary to again achieve maximal control, as in initial therapy (see Section 5.3.3.7). Thus, overall drug exposures in most patients may not be substantially less than maintenance therapy.

### 5.3.3.5 Efficacy With Self-administration

The efficacy of self-administration was evaluated during the randomized withdrawal period since it represented a controlled portion of the study. Subjects were encouraged to self-administer study agent beginning at Week 12. Among subjects randomized at Week 40, approximately 60% of subjects self-administered ustekinumab or placebo, while study agent was administered in approximately 40% by a health care professional. Maintenance of response was consistent whether ustekinumab was self-administered or health care professional-administered (see Figure 13). In T09, efficacy was also consistent whether ustekinumab was self-administered or health care professional-administered.



**Figure 13** Percent of subjects achieving PASI 75 response from Week 40 through Week 56 by self versus healthcare professional administration at Week 40; subjects randomized at Week 40 in T08

### 5.3.3.6 Dose Interval Adjustment

In T08, approximately 40% to 50% of Week 28 partial responders achieved a PASI 75 response after dosing interval adjustment to q8w, and this proportion of PASI 75 responders was maintained over time through Week 56. Moreover, approximately 15% to 20% of subjects in all groups achieved and maintained a PASI 90 response, and

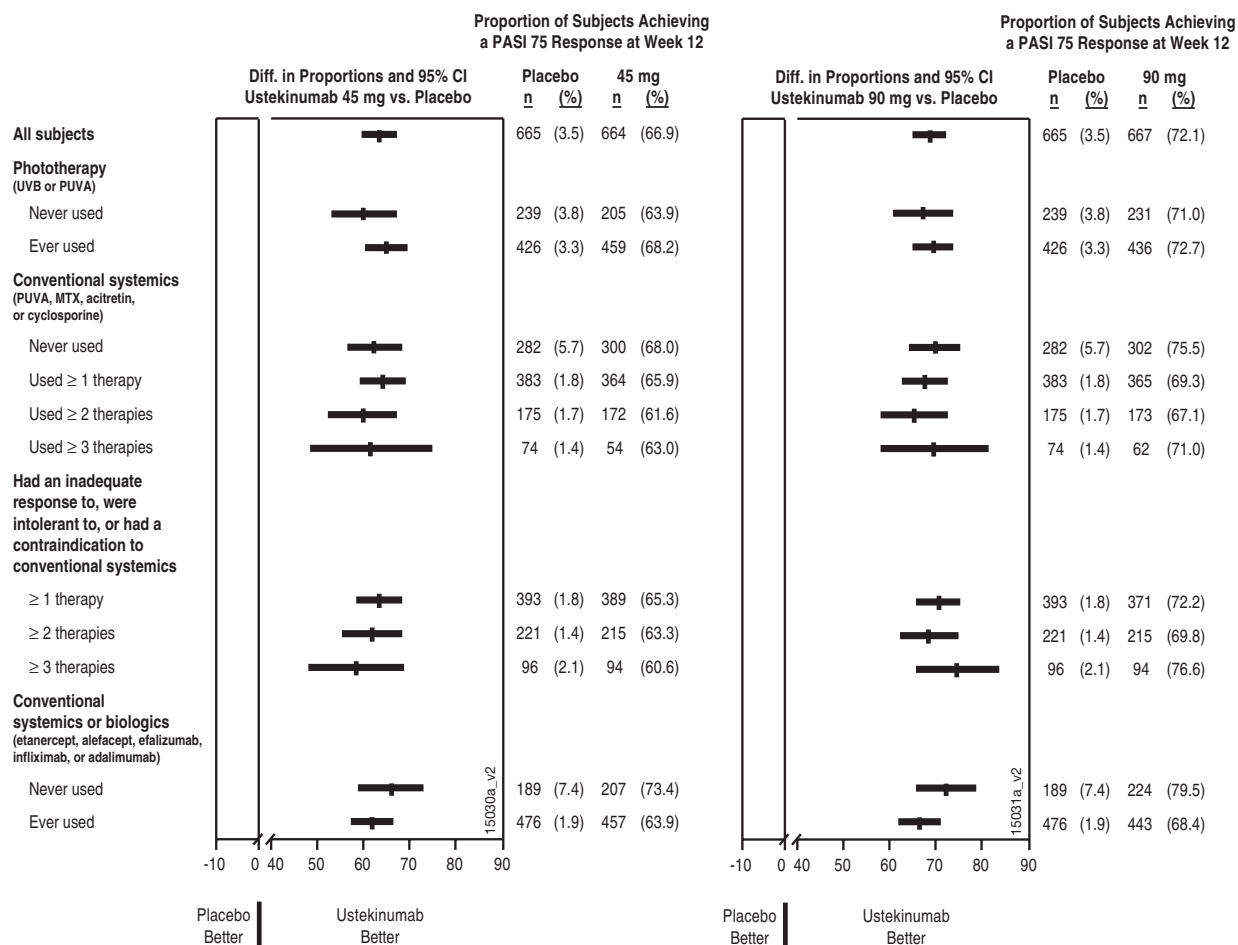
approximately 80% maintained at least a PASI 50 response. Similar observations were seen in subjects inadequately responding at Week 40 who had their dosing interval adjusted to q8w.

#### **5.3.3.7     Retreatment**

In T08, subjects withdrawn from therapy at Week 40 were retreated with their original ustekinumab regimen when they experienced loss of therapeutic effect (defined as loss of  $\geq 50\%$  of their Week 40 PASI improvement). Response to retreatment was comparable across both dose groups. Within 4 and 8 weeks of reinitiation of therapy, 43.6% and 76.2% of the subjects withdrawn from therapy, respectively, achieved a PASI 75 response. The results demonstrate that after retreatment with 2 doses of ustekinumab, the majority of subjects achieved a PASI 75 response within 8 weeks.

#### **5.3.3.8     Improvement in Psoriasis Across Subpopulations**

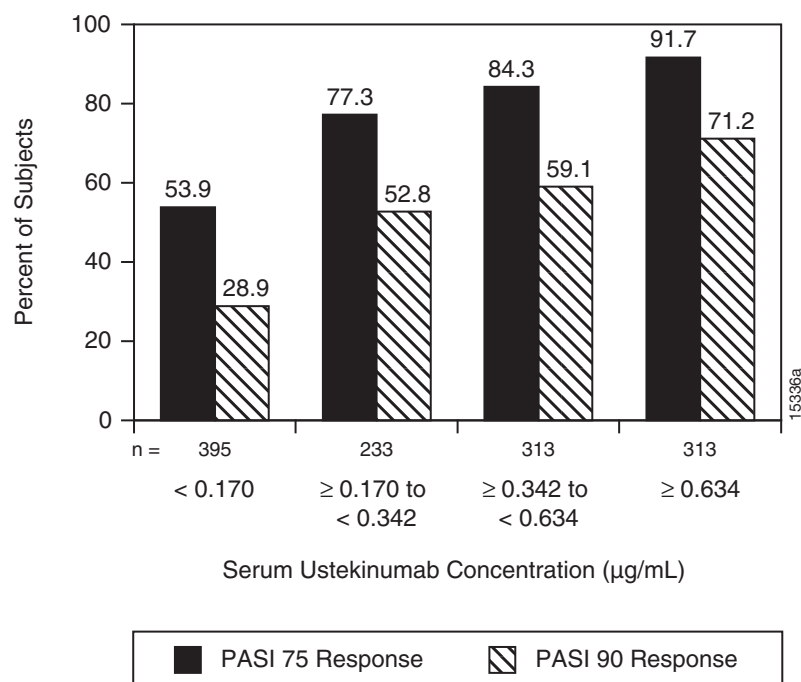
Ustekinumab 45 mg and 90 mg consistently demonstrated high levels of efficacy in all subpopulations, and efficacy was not impacted by demographic features (including subjects  $\geq 65$  years old), clinical disease characteristics (including subjects with a history of PsA), or psoriasis medication history (see Figure 14).



**Figure 14** Difference (vertical bars) and 95% CI (horizontal bars) for comparing proportion of subjects achieving a PASI 75 response at Week 12 for subgroups defined by psoriasis medication history in Phase 3: (left) ustekinumab 45 mg group versus placebo group (right); 90 mg group versus placebo group

### 5.3.3.9 Association of Clinical Response with Pharmacokinetics

Clinical response was generally associated with serum ustekinumab levels. Higher clinical response rates were observed in subjects who had higher median serum concentrations than in subjects with lower median serum concentrations. Data pooled from the Phase 3 studies showed a concentration-response relationship at Week 28. As trough serum concentration increased, a greater proportion of subjects achieved PASI 75 and PASI 90 responses (Figure 15).



**Figure 15** Subjects achieving PASI 75 and PASI 90 responses at Week 28 by trough serum ustekinumab concentrations at Week 28 in psoriasis Phase 3; treated subjects randomized to ustekinumab at Week 0

#### 5.3.3.9.1 Impact of Weight on Clinical Response

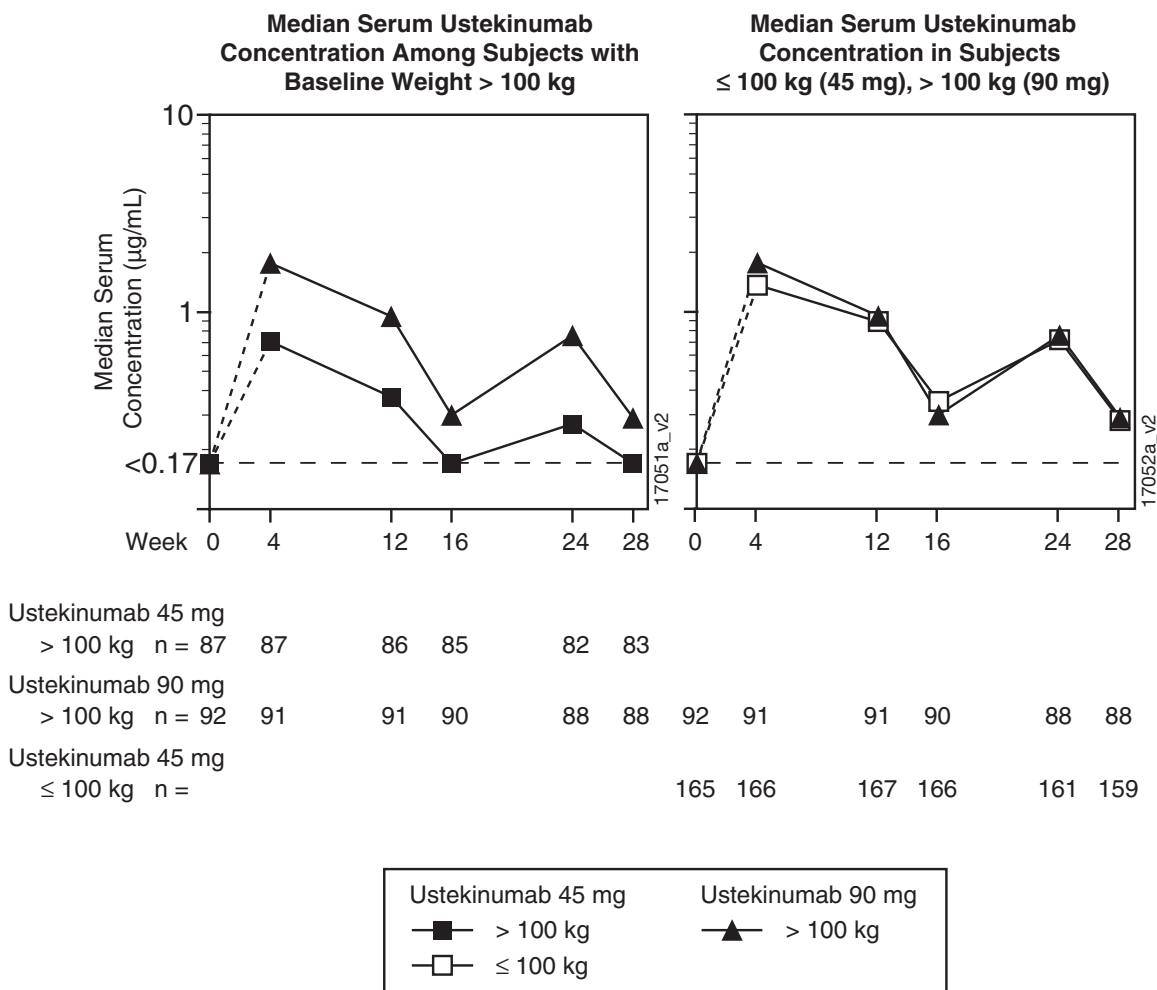
Since pharmacokinetics were impacted by weight (see Section 4.4.5), clinical response was also impacted by weight, most notably in the 45 mg group. In prespecified analyses, efficacy was evaluated by weight categories in 10 kg increments (eg, 51 to  $\leq 60$  kg, 61 to  $\leq 70$  kg, etc). Based on these analyses, there was a natural “inflection point” at 100 kg, evident in both studies, such that in the subpopulation of subjects  $> 100$  kg, PASI 75 response rates were approximately 15 to 20 percentage points higher (in absolute terms) with 90 mg dosing compared with 45 mg dosing at Weeks 12 and 28 (see Table 8). Below this threshold (ie, in subjects  $\leq 100$  kg), response rates were generally similar between the 45 mg and 90 mg groups. Similar results were seen when response was evaluated by PGA.



**Table 8 Summary of PASI 75 response by weight category; randomized subjects in Phase 3**

	T08		T09	
	45 mg	90 mg	45 mg	90 mg
Subjects randomized	255	256	409	411
PASI 75 responders				
Week 12				
≤ 100 kg	73.8% (124/168)	65.2% (107/164)	73.4% (218/297)	77.9% (225/289)
> 100 kg	54.0% (47/87)	68.5% (63/92)	49.1% (55/112)	71.1% (86/121)
Week 28				
≤ 100 kg	79.3% (130/164)	81.0% (124/153)	75.6% (217/287)	80.7% (226/280)
> 100 kg	55.8% (48/86)	74.4% (67/90)	53.6% (59/110)	73.9% (88/119)

As expected, with a drug that demonstrates dose proportional kinetics, among subjects with weight > 100 kg, serum concentrations were lower in subjects who received 45 mg compared to 90 mg. Additionally in subjects who received 45 mg, the median drug levels were below the lower level of detection at trough concentrations. However, the serum concentrations in subjects who received 90 mg with weight > 100 kg were consistent with subjects who received 45 mg with weight ≤ 100 kg (see Figure 16). Notably, at Week 28, subjects who received 45 mg and were ≤ 100 kg had efficacy rates of approximately 76% to 79% compared to subjects who were > 100 and received 90 mg with efficacy rates of approximately 74% to 75%. Therefore, fixed dosing by weight (45 mg ≤ 100 kg, 90 mg > 100 kg) allows equivalent PK exposure and similar efficacy in both weight categories.



**Figure 16** Median serum ustekinumab concentrations (micrograms/mL) in subjects > 100 kg (45 mg) and > 100 kg (90 mg) (left panel), ≤ 100 kg (45 mg) and > 100 kg (90 mg) (right panel); treated subjects randomized to ustekinumab at Week 0 in T08

In summary:

- There was a correlation between improved clinical response and higher ustekinumab serum concentrations.
- Efficacy was lower in subjects > 100 kg who received the 45 mg dose compared to those who received 90 mg and this was consistent with lower serum concentrations in those that received 45 mg.
- Subjects > 100 kg who received 90 mg had equivalent serum concentrations when compared to subjects ≤ 100 kg who received 45 mg and had similar efficacy.

### **5.3.3.10 Association of Antibodies to Ustekinumab and Efficacy**

The rate of positive antibodies was low; therefore, the overall effect of antibodies on efficacy was limited.

### **5.3.3.11 Improvement in Patient-Reported Outcomes**

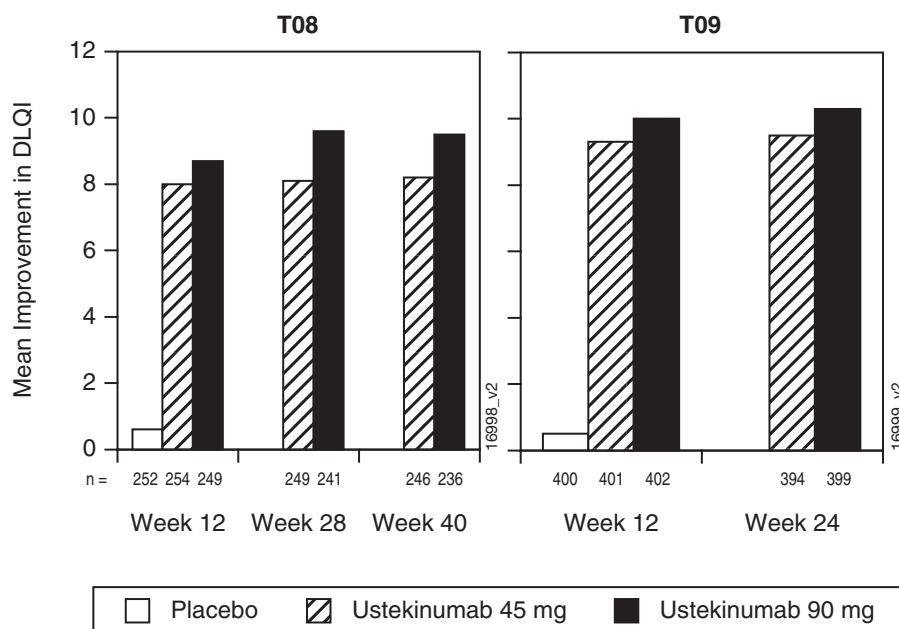
In addition to evaluating treatment effect using physician assessment instruments, it is important to assess the patient's perspective of the treatment effect using patient-reported outcome measures. Multiple patient-reported outcomes including both disease-specific and general outcomes were employed in T08 and T09. Baseline measurements for all patient-reported outcomes instruments were well balanced across the placebo and active treatment groups. Across all measures, significant responses were observed at Week 12. Additionally, for selected measures evaluated beyond Week 12, responses were maintained through the course of the studies.

#### **5.3.3.11.1 Disease-Specific Outcomes**

##### **DLQI**

Skin disease-specific quality of life was assessed with the DLQI in both T08 and T09. Possible DLQI scores range from 0 to 30, with lower scores indicating better QOL (a DLQI of 0 indicates no detectable impairment on patients' quality of life). At baseline, subjects had impaired quality of life with a mean DLQI of 11.5 and 12.3 in T08 and T09, respectively. A mean DLQI score of 0.5 ( $\pm$  1.1) was reported for healthy control subjects in the UK ([Finlay and Khan, 1994](#)).

Subjects treated with ustekinumab 45 mg and 90 mg demonstrated significant and clinically meaningful improvements in DLQI at Week 12 (see Figure 17).



**Figure 17 Mean improvement in DLQI; subjects randomized at Week 0 in T08 and T09**

- Significant improvement in DLQI scores was observed at the earliest measured timepoint in each study (ie, Week 2 in T08 and Week 4 in T09).
- A high proportion of subjects in each ustekinumab group achieved a reduction of 5 or more points in DLQI score at Week 12, indicating a clinically meaningful improvement in quality of life (see Table 9; [Kimball et al, 2004](#)).
- A significantly greater proportion of subjects receiving ustekinumab compared with placebo achieved a DLQI score of 0 at Week 12, indicating no detectable impairment on patients' quality of life (see Table 9).
- Improvements in DLQI scores in the ustekinumab groups were maintained through Week 40 (eg, beginning of the randomized withdrawal period in T08).

**Table 9 Summary of DLQI endpoints in Phase 3**

		<u>T08</u>			<u>T09</u>	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Subjects randomized	255	255	256	410	409	411
DLQI score of 0 at Week 12 <sup>a</sup>	0.8%	32.7%	34.0%	1.0%	36.7%	39.1%
Reduction of 5 or more points from baseline in DLQI score at Week 12 <sup>a</sup>	17.9%	64.6%	71.1%	21.4%	71.8%	76.9%

<sup>a</sup> p < 0.001 for each ustekinumab group vs placebo comparison.

- In subjects randomized to maintenance therapy during the randomized withdrawal period, the improvements in DLQI scores from baseline were further maintained through Week 52 in both groups. In subjects withdrawn from therapy at Week 40, a worsening in DLQI was observed at Week 52, indicating quality of life impairment after just 1 missed dose.

### **Itch VAS**

Pruritus is a common symptom associated with psoriasis that affects patients' quality of life. Pruritus was assessed using the Itch VAS (a 0 – 10 scale wherein 0 indicates no itch at all and 10 indicates severe itch) at Weeks 0 and 12. At baseline, mean VAS scores were 7.0, 6.7, and 6.7 for the placebo, 45 mg, and 90 mg groups, respectively.

- For subjects randomized to placebo, the mean change in itch severity from baseline to Week 12 was –0.78, compared to subjects in the ustekinumab 45 mg and 90 mg groups, –4.91 and –5.14, respectively (p < 0.001 for both comparisons vs placebo).

### **5.3.3.11.2 General Patient-Reported Outcomes**

#### **SF-36**

The SF-36 was used to assess patients' overall quality of life (higher scores indicate better quality of life). This instrument has been used broadly across numerous disease states and in many clinical studies and has well-documented psychometric properties (eg, validity, reliability, and sensitivity) across 8 domains. Mean baseline Physical Component Summary scores were 47.2, 48.9, and 47.5, and mean baseline Mental Component Summary scores were 49.6, 50.0, and 49.9 for the placebo, 45 mg, and 90 mg groups, respectively.

- 
- Compared with placebo, each ustekinumab group had significantly greater improvements from baseline in both the Physical Component Summary score (2.0 and 3.2, versus -0.5,  $p < 0.001$ ) and Mental Component Summary score (2.1 and 2.5 versus -1.3,  $p < 0.001$ ) at Week 12.
  - All 8 domains of the SF-36, including physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health showed statistically significant improvements in each of the ustekinumab groups versus placebo at Week 12 ( $p \leq 0.017$ ).
  - The improvements in both SF-36 summary scores observed at Week 12 were generally maintained through Week 40 (eg, beginning of the randomized withdrawal period) in both ustekinumab groups.

### **HADS**

The HADS, an instrument to assess patients' anxiety and depression, was used since much previous research demonstrates that psoriasis patients suffer from a higher incidence of psychiatric disorders than the general population ([Gottlieb et al, 2008](#)). Baseline mean anxiety scale (HADS-A) scores were 7.0, 6.8, and 6.8 and mean depression scale (HADS-D) scores were 4.9, 4.9, and 5.4 for the placebo, 45 mg, and 90 mg groups, respectively.

- Compared with placebo, each ustekinumab group had significantly greater improvements in both anxiety and depression from baseline to Week 12. In the anxiety scale (HADS-A), the 45 mg and 90 mg groups showed significant mean improvement compared with placebo (1.6 and 1.6 versus 0.1,  $p < 0.001$ ). Similarly, in the depression scale (HADS-D), the 45 mg and 90 mg groups showed significant improvement compared with placebo (1.7 and 2.1 versus -0.2,  $p < 0.001$ ).
- The improvements in anxiety and depression observed at Week 12 in each ustekinumab group were maintained at Week 24, the last timepoint at which HADS data were collected.

### **WLQ**

Previous research suggests that psoriasis has a substantial negative impact on subjects' careers and overall work productivity ([Schmitt and Ford, 2006](#)). The WLQ was used in T09 in order to measure work limitations in performing specific job demands, including Physical demands, Time Management demands, Mental Interpersonal demands, and Output demands.

- Compared with placebo, subjects in each ustekinumab group showed significant improvement in work limitations from baseline to Week 12; this improvement was observed across all 4 scales of the WLQ except in the 90 mg group for the Physical Demands scale ( $p = 0.06$ ).
- The improvements observed in the ustekinumab groups at Week 12 were generally maintained at Week 24.

### **Productivity VAS**

Since research suggests that productivity is negatively affected by psoriasis, the Productivity VAS was used in the T08 and T09 studies. Productivity was measured on a 0 to 10 scale, with lower scores indicating greater productivity. At baseline, mean VAS scores for T08 were 3.2, 3.0, and 3.2 for the placebo, 45 mg, and 90 mg groups, respectively. Mean VAS for T09 at baseline were 3.7, 3.8, and 4.0 for the placebo, 45 mg, and 90 mg groups, respectively. Significantly greater improvements in productivity were observed in both the T08 and T09 studies for each ustekinumab group versus placebo.

- In T08, the mean change in productivity from baseline to Week 12 was  $-1.8$  in the 45 mg group and  $-2.2$  in the 90 mg group, compared with  $0.2$  in the placebo group.
- In T09, the mean change in productivity from baseline to Week 12 was  $-2.5$  in the 45 mg group and  $-2.6$  in the 90 mg group, compared with  $-0.1$  in the placebo group.

### **5.3.3.11.3 Summary of Patient-Reported Outcomes**

- Compared with placebo, subjects randomized to ustekinumab in the T08 and T09 studies achieved significantly greater improvements in numerous patient-reported outcome measures including quality of life, pruritus, anxiety, depression, productivity, and work limitations.
- Significant improvements were achieved by each ustekinumab group for every patient-reported outcome measure at the earliest timepoint measured in each study except for the WLQ Physical Demands scale for the 90mg group at Week 12.
- Improvements were maintained for all patient-reported outcomes with continued maintenance therapy for up to 52 weeks.

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## 6 Summary and Conclusions on Efficacy

Three adequate and well-controlled studies demonstrated the efficacy of ustekinumab (45 mg or 90 mg) in the treatment of moderate to severe plaque psoriasis. These studies demonstrated the following:

- Ustekinumab had high efficacy in improving moderate to severe plaque psoriasis as demonstrated by the PASI, PGA, and NAPSI.
- Ustekinumab continued to show efficacy with long-term maintenance therapy for at least 1 year in a randomized withdrawal analysis.
  - PASI 75 response was generally maintained through at least 1 year in subjects receiving q12w maintenance therapy. This maintenance was significantly superior to that observed in subjects randomized to crossover to placebo ( $p < 0.001$  by log rank test; using a randomized withdrawal design).
  - Efficacy was observed across multiple PASI and PGA endpoints.
- Ustekinumab consistently demonstrated high levels of efficacy in all subpopulations including subgroups defined by demographics, disease characteristics, and previous therapies.
- Improvement in psoriasis and serum concentration were impacted by weight:
  - In subjects with weight  $> 100$  kg, the 90 mg dose was more effective compared with the 45 mg dose.
  - Subjects with weight  $> 100$  kg in the 90 mg group achieved median trough serum levels of ustekinumab and PASI 75 and PGA response rates that were generally comparable to those observed in subjects with weight  $\leq 100$  kg in the 45 mg group.
- Ustekinumab improved both disease-specific and general patient-reported outcomes:
  - Quality of life as measured by both the DLQI and SF-36
  - Pruritus as measured by the Itch VAS
  - Anxiety and depression as measured by the HADS
  - Work limitations as measured by the WLQ
  - Productivity as measured by the Productivity VAS.



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## 7 Safety and Tolerability

### 7.1 Background

To evaluate the safety of ustekinumab, AEs and laboratory assessments were captured in each clinical study. Adverse events (including clinically important laboratory abnormalities as judged by the investigator) were categorized by the investigator for seriousness using regulatory criteria, severity using functional criteria, and investigator opinion for relationship. Adverse events were coded by system-organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

The safety of ustekinumab was evaluated by two general analytical approaches:

- Analyses of rates of AEs during the placebo-controlled periods of the studies;
- Analyses of rates of AEs over the entire observation period with adjustment for time of observation (ie, per 100 subject-years of follow-up).

Analyses of safety in the target patient population included all safety data from the Phase 2 and 3 psoriasis studies (unless otherwise stated), which recruited similar populations of subjects (ie, moderate to severe plaque psoriasis defined by similar eligibility criteria) and studied identical doses (45 mg and 90 mg fixed doses). The Phase 2 and 3 studies provided approximately 13% and 85% of the subjects exposed to ustekinumab in the psoriasis clinical study program, respectively.

In addition to general analyses of safety, additional analyses were conducted on targeted AEs based on ustekinumab mechanism of action and specific risks in the target patient population. Targeted events included:

- Infection and malignancy because ustekinumab blocks IL-12 and IL-23 bioactivity, with potential downstream impact on the immune system and immunosurveillance;
- Asthma and atopic diseases because of ustekinumab's theoretical potential to block differentiation of Th1 cells leading to greater polarization of immune responses towards a Th2 phenotype;
- Cardiovascular disease because patients with psoriasis have high rates of comorbidities associated with cardiovascular risk (eg, hypertension, obesity, and diabetes), and patients with psoriasis, especially those with severe psoriasis, have been reported to be at increased risk of atherosclerotic cardiovascular diseases ([McDonald and Calabresi, 1978](#); [Gelfand et al, 2006a](#); [Mallbris et al, 2004](#)).
- Psoriasis and PsA because some other systemic therapeutics have paradoxically been associated with worsening of these diseases (see Table 1).

When informative, safety event rates observed in clinical studies were compared with expected rates based on analyses of external database. The external databases selected to estimate expected event rates of targeted events are described in [Appendix D](#).

## 7.2 Subjects Included in the Integrated Analysis of Safety

The majority of safety experience with ustekinumab derives from clinical studies in psoriasis. Across all indications studied with ustekinumab (psoriasis, PsA, Crohn's disease, and MS), a total of 2713 subjects have been treated with ustekinumab (see Table 10).

**Table 10 Subjects treated with ustekinumab across indications through the data cutoff for the BLA**

	Psoriasis Studies <sup>a</sup>	PsA Study <sup>a</sup>	Crohn's Disease Study <sup>a</sup>	Multiple Sclerosis Studies <sup>a</sup>	All Studies <sup>a</sup>
Subjects treated with ustekinumab	2301 (84.8%)	76 (2.8%)	120 (4.4%)	216 (8.0%)	2713
Total subject-years of follow-up	1480 (87.4%)	18 (1.1%)	52 (3.1%)	144 (8.5%)	1694

<sup>a</sup> Psoriasis Studies include T01, T02, T04, T08 (Week 52), and T09 (Week 28). PsA Study includes T10 (Week 12). Crohn's Disease Study includes T07. Multiple Sclerosis Studies include T03 and T06.

Extracted from RE302:[S\_EXP\_31\_A], 18JUN2007 15:43; RE302:[S\_DTH\_10\_D], 03JUL2007 15:10

The integrated analyses of safety focus primarily on the Phase 2 and Phase 3 placebo-controlled clinical studies of psoriasis, and additional supportive information on the safety of ustekinumab was provided by analyses of the safety experience in two Phase 1 psoriasis studies, as well as studies in other indications, including PsA, Crohn's disease, and MS.

### 7.2.1 Safety in Target Population

Safety data discussed in this section pertain to data from the pooled Phase 2 and Phase 3 studies (unless otherwise stated) in subjects with moderate to severe plaque psoriasis.

#### 7.2.1.1 Safety Population and Extent of Exposure

A total of 2266 subjects have been treated with ustekinumab through the data cutoff for the BLA in Phase 2 and Phase 3 studies in psoriasis (T04, T08, and T09). Of these, 1582 subjects received ustekinumab during the placebo-controlled periods.

In the initial BLA, long-term safety is supported by data from 1602 subjects who received at least 6 months of ustekinumab treatment and 362 subjects exposed for at least 1 year (see Table 11). The safety of ustekinumab through this period (the data cutoff for the BLA) is presented in Section 7.2 through Section 7.4

**Table 11 Summary of duration of ustekinumab exposure in Phase 2 and Phase 3 through the data cutoff for the BLA**

	Ustekinumab		
	45 mg	90 mg	Combined
Subjects treated with ustekinumab	1110	1156	2266
Duration of ustekinumab exposure			
At least 6 months <sup>a</sup>	812 (73.2%)	790 (68.3%)	1602 (70.7%)
At least 1 year <sup>b</sup>	191 (17.2%)	171 (14.8%)	362 (16.0%)

<sup>a</sup> The duration between the first and last ustekinumab administration was at least 14 weeks.

<sup>b</sup> The duration between the first and last ustekinumab administration was at least 38 weeks.

Extracted from RE302:[S\_EXP\_13\_B], 18JUN2007 15:43

With additional safety data provided in the 120-day safety update, 1970 subjects were exposed for at least 6 months, 1285 subjects were exposed for at least 1 year, and 373 subjects were exposed for at least 18 months (see Table 12). The safety of ustekinumab through this period (the data cutoff for the 120-day safety update) is presented in Section 7.5.

**Table 12 Summary of duration of ustekinumab exposure in Phase 2 and Phase 3 through the data cutoff for the 120-day safety update**

	Ustekinumab		
	45 mg	90 mg	Combined
Subjects treated with ustekinumab	1110	1156	2266
Duration of ustekinumab exposure			
At least 6 months <sup>a</sup>	994 (89.5%)	976 (84.4%)	1970 (86.9%)
At least 1 year <sup>b</sup>	645 (58.1%)	640 (55.4%)	1285 (56.7%)
At least 18 months <sup>c</sup>	187 (16.8%)	186 (16.1%)	373 (16.5%)

<sup>a</sup> The duration between the first and last ustekinumab administration was at least 14 weeks.

<sup>b</sup> The duration between the first and last ustekinumab administration was at least 38 weeks.

<sup>c</sup> The duration between the first and last ustekinumab administration was at least 62 weeks.

Extracted from RE333:[S\_EXP\_13\_B], 20DEC2007 8:42

Targeted AEs that occurred at low frequency were examined using data combined from the controlled portions of the Phase 2 and 3 studies, as well as from all available data from the Phase 2 and 3 studies. Incidence rates for these events are presented per hundred subject-years of observation. In the controlled portions of the Phase 2 and 3 studies, there are 177 subject-years of observation for subjects who received placebo and 407 subject-years of observation for subjects who received ustekinumab. All available safety data from the Phase 2 and 3 studies includes 182 subject-years of observation for subjects who received placebo and 1467 subject-years of observation for subjects who received ustekinumab. Because analyses using all available safety data included observation periods that were not concurrent and the average observation time per subject differed between treatment groups, results of the incidence rate analyses should be interpreted with caution.

Given the 1582 subjects exposed to ustekinumab in the placebo-controlled period of the Phase 2 and 3 studies, the likelihood of observing at least 1 AE during a 12-week treatment period with a true incidence of 1% is almost 100% and the likelihood of observing an event with a true incidence of 0.1% is 79%. Similarly, the likelihood of observing an AE with a true incidence of 1% or 0.1% through the data cutoff for the BLA for the 2266 ustekinumab-treated subjects is almost 100% and 90%, respectively.

An impact of ustekinumab on rare safety events cannot be excluded, though for events not observed in the clinical studies, the size of the clinical database allows us to be 97.5% confident that such events would occur at a rate of 0.16% or lower within the follow-up captured in the database.

### **7.2.1.2 Baseline Demographics and Comorbidities in the Target Population**

Baseline demographics and comorbidities in each of the Phase 2 and 3 studies were balanced between treatment groups. Consistent with psoriasis clinical studies of other biologic agents ([Leonardi et al, 2003](#); [Lebwohl et al, 2003a](#); [Lebwohl et al, 2003b](#); [Menter et al, 2008](#)), a majority of subjects were male (68.8%; see Table 13) and Caucasian (92.5% overall). The higher overall reported rates of obesity (48.8%), hypertension (27.3%), hyperlipidemia (20.3%), diabetes (11.0%), current smoking (31.9%), and depression (14.6%) are consistent with previous reports of associated comorbidities as well as observations in previous psoriasis clinical studies ([Gordon et al, 2006](#); [Menter et al, 2007](#), [Alexander et al, 2001](#); [Neimann et al, 2006](#); [Pearce et al, 2005](#)).

**Table 13 Baseline demographics and selected medical history in Phase 2 and Phase 3**

	T04 <sup>a</sup>	T08	T09	Combined Studies
Subjects randomized at Week 0	320	766	1230	2316
<i>Demographics</i>				
Gender - Male	222 (69.4%)	531 (69.3%)	840 (68.3%)	1593 (68.8%)
Caucasian	297 (92.8%)	717 (93.6%)	1128 (91.7%)	2142 (92.5%)
Age (Mean yrs $\pm$ SD)	44.9 $\pm$ 13.19	45.3 $\pm$ 11.71	46.2 $\pm$ 12.24	45.7 $\pm$ 12.21
Weight (Mean kg $\pm$ SD)	92.96 $\pm$ 22.744	93.88 $\pm$ 23.685	90.99 $\pm$ 21.278	92.22 $\pm$ 22.334
BMI				
Normal (< 25)	50 (15.7%)	118 (15.4%)	245 (19.9%)	413 (17.8%)
Overweight (25 to < 30)	120 (37.6%)	262 (34.2%)	390 (31.7%)	772 (33.4%)
Obese ( $\geq$ 30)	149 (46.7%)	386 (50.4%)	594 (48.3%)	1129 (48.8%)
<i>Cardiovascular disease or risk factors</i>				
Ischemic heart disease/ coronary artery disease	12 (3.8%)	25 (3.3%)	51 (4.1%)	88 (3.8%)
Peripheral vascular disease	NA	5 (0.7%)	15 (1.2%)	20 (1.0%)
Transient ischemic attack	NA	5 (0.7%)	12 (1.0%)	17 (0.9%)
Stroke	NA	4 (0.5%)	8 (0.7%)	12 (0.6%)
Diabetes mellitus	38 (11.9%)	91 (11.9%)	125 (10.2%)	254 (11.0%)
Hyperlipidemia	48 (15.0%)	170 (22.2%)	253 (20.6%)	471 (20.3%)
Hypertension	78 (24.4%)	218 (28.5%)	337 (27.4%)	633 (27.3%)
Smoking (past or current)	NA	452 (59.0%)	777 (63.2%)	1229 (61.6%)
Current smoking	NA	242 (31.6%)	395 (32.1%)	637 (31.9%)
Family history of early coronary artery disease (< 55 years of age)	NA	101 (13.2%)	132 (10.7%)	233 (11.7%)
<i>Th2-mediated diseases</i>				
Asthma	NA	68 (8.9%)	92 (7.5%)	160 (8.0%)
Seasonal allergy/hayfever	NA	194 (25.3%)	256 (20.8%)	450 (22.5%)
<i>Other</i>				
Psoriatic arthritis	62 (19.4%)	258 (33.7%)	305 (24.8%)	625 (27.0%)
Skin cancer	7 (2.2%)	12 (1.6%)	22 (1.8%)	41 (1.8%)
Basal cell cancer	6 (1.9%)	12 (1.6%)	16 (1.3%)	34 (1.5%)
Squamous cell cancer	2 (0.6%)	1 (0.1%)	6 (0.5%)	9 (0.4%)
Depression	35 (10.9%)	121 (15.8%)	181 (14.7%)	337 (14.6%)
Alcohol intake (past or current)	NA	481 (62.8%)	760 (61.8%)	1241 (62.2%)

<sup>a</sup> NA = Not collected in the Phase 2 study.

Extracted from 302:[P\_BDIS\_9\_A], 22JUN2007 14:30; RE302:[P\_DEM\_12\_A], 18JUN2007 15:36

### 7.2.1.3 All Adverse Events

The proportions of subjects who experienced at least 1 AE through Week 12 (see Table 14 for events occurring in at least 1% of subjects) was 50.4% in the placebo group, 57.6% in the 45 mg group, and 51.6% in the 90 mg group. Infections and infestations were the most frequently reported class of AEs, which occurred in 23.0% of subjects in the placebo group, 26.6% in the 45 mg group, 25.1% in the 90 mg group. Adverse events that occurred in more than 5% of subjects in the combined group included nasopharyngitis, upper respiratory tract infection, and headache. Common AEs that occurred in at least 1% of ustekinumab-treated subjects and at least 1.5-fold more frequently than observed in placebo-treated subjects included dizziness, back pain, myalgia, injection-site erythema, ecchymosis, diarrhoea and pharyngolaryngeal pain. Common AEs tended to be mild and self-limited.

The system-organ class with the greatest disparity in event rates between ustekinumab-treated versus placebo-treated subjects was general disorders and administration site conditions (9.1% versus 5.3%, respectively). This was in part influenced by injection-site reactions. Injection-site erythema was the most frequently reported injection site reaction (1.3%) in ustekinumab-treated subjects compared with 0.4% of placebo-treated subjects.

**Table 14 Adverse events reported with frequency of 1% or greater in ustekinumab-treated subjects through Week 12 in Phase 2 and Phase 3**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated	732	790	792	1582
Subjects with 1 or more adverse events	369 (50.4%)	455 (57.6%)	409 (51.6%)	864 (54.6%)
MedDRA system-organ class/preferred term				
Infections and infestations	168 (23.0%)	210 (26.6%)	199 (25.1%)	409 (25.9%)
Nasopharyngitis	58 (7.9%)	66 (8.4%)	63 (8.0%)	129 (8.2%)
Upper respiratory tract infection	32 (4.4%)	45 (5.7%)	41 (5.2%)	86 (5.4%)
Sinusitis	11 (1.5%)	11 (1.4%)	10 (1.3%)	21 (1.3%)
Gastroenteritis	9 (1.2%)	12 (1.5%)	6 (0.8%)	18 (1.1%)
Influenza	5 (0.7%)	8 (1.0%)	7 (0.9%)	15 (0.9%)
Viral upper respiratory tract infection	2 (0.3%)	8 (1.0%)	5 (0.6%)	13 (0.8%)
Nervous system disorders	58 (7.9%)	74 (9.4%)	78 (9.8%)	152 (9.6%)
Headache	33 (4.5%)	45 (5.7%)	47 (5.9%)	92 (5.8%)
Dizziness	8 (1.1%)	9 (1.1%)	18 (2.3%)	27 (1.7%)

**Table 14 Adverse events reported with frequency of 1% or greater in ustekinumab-treated subjects through Week 12 in Phase 2 and Phase 3**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Musculoskeletal and connective tissue disorders	72 (9.8%)	81 (10.3%)	67 (8.5%)	148 (9.4%)
Arthralgia	21 (2.9%)	27 (3.4%)	24 (3.0%)	51 (3.2%)
Back pain	8 (1.1%)	16 (2.0%)	15 (1.9%)	31 (2.0%)
Myalgia	6 (0.8%)	11 (1.4%)	11 (1.4%)	22 (1.4%)
General disorders and administration site conditions	39 (5.3%)	68 (8.6%)	76 (9.6%)	144 (9.1%)
Fatigue	15 (2.0%)	22 (2.8%)	22 (2.8%)	44 (2.8%)
Injection site erythema	3 (0.4%)	8 (1.0%)	13 (1.6%)	21 (1.3%)
Skin and subcutaneous tissue disorders	55 (7.5%)	69 (8.7%)	63 (8.0%)	132 (8.3%)
Pruritus	10 (1.4%)	17 (2.2%)	14 (1.8%)	31 (2.0%)
Psoriasis	16 (2.2%)	3 (0.4%)	10 (1.3%)	13 (0.8%)
Ecchymosis	2 (0.3%)	3 (0.4%)	8 (1.0%)	11 (0.7%)
Gastrointestinal disorders	48 (6.6%)	61 (7.7%)	63 (8.0%)	124 (7.8%)
Diarrhoea	12 (1.6%)	20 (2.5%)	18 (2.3%)	38 (2.4%)
Nausea	11 (1.5%)	12 (1.5%)	12 (1.5%)	24 (1.5%)
Respiratory, thoracic and mediastinal disorders	32 (4.4%)	44 (5.6%)	47 (5.9%)	91 (5.8%)
Pharyngolaryngeal pain	7 (1.0%)	10 (1.3%)	13 (1.6%)	23 (1.5%)
Cough	11 (1.5%)	8 (1.0%)	10 (1.3%)	18 (1.1%)
Nasal congestion	3 (0.4%)	8 (1.0%)	5 (0.6%)	13 (0.8%)
Psychiatric disorders	11 (1.5%)	22 (2.8%)	18 (2.3%)	40 (2.5%)
Depression	3 (0.4%)	9 (1.1%)	5 (0.6%)	14 (0.9%)
Insomnia	5 (0.7%)	8 (1.0%)	4 (0.5%)	12 (0.8%)
Vascular disorders	14 (1.9%)	19 (2.4%)	16 (2.0%)	35 (2.2%)
Hypertension	11 (1.5%)	13 (1.6%)	8 (1.0%)	21 (1.3%)

Extracted from RE302:[S\_AE\_61\_A], 02AUG2007 10:05

To evaluate AEs over the entire observation period (ie, through the data cutoff for the BLA), AE rates per hundred subject-years of follow-up were evaluated (see Table 15 for AEs that occurred at a rate of at least 5 per hundred subject-years of follow-up in ustekinumab-treated subjects). In these analyses, each AE reported in an individual subject was counted separately. Since the average follow-up varies across groups, AEs that do not occur at a constant (linear) rate should be interpreted with caution (eg, events with seasonal variability). This is particularly true in interpreting event rates among

subjects in the placebo group, in whom only 13.4% of follow-up occurred during influenza season (November through March).

**Table 15 Adverse events reported with frequency of at least 5 per hundred subject-years of follow-up in ustekinumab-treated subjects through the data cutoff for the BLA in Phase 2 and Phase 3**

	Placebo	Ustekinumab				
		Placebo → 45 mg <sup>a</sup>	Placebo → 90 mg <sup>a</sup>	45 mg	90 mg	Combined
Subjects treated	732	320	364	790	792	2266
Avg duration of follow-up (weeks)	12.9	26.4	25.2	37.0	37.2	33.7
Number of adverse events per hundred subject-years of follow-up	406	360	288	391	385	373
MedDRA system-organ class/preferred term						
Infections and infestations						
Nasopharyngitis	35.7	40.7	27.8	30.8	33.9	32.7
Upper respiratory tract infection	21.4	23.4	24.4	27.0	25.1	25.6
Influenza	2.7	11.1	6.2	5.9	6.4	6.7
Sinusitis	6.0	6.2	2.8	5.7	7.6	6.1
Gastroenteritis	4.9	4.3	5.7	6.0	5.8	5.7
Musculoskeletal and connective tissue disorders						
Arthralgia	12.6	4.9	6.2	10.5	9.2	8.9
Back Pain	4.4	4.9	4.0	7.1	6.5	6.3
Gastrointestinal disorders						
Diarrhoea	7.1	2.5	4.0	6.2	6.0	5.5
Nervous system disorders						
Headache	25.3	12.3	6.2	16.4	18.6	15.5
General disorders and administration site conditions						
Fatigue	8.8	4.9	2.8	7.1	4.6	5.4

<sup>a</sup> Placebo subjects who crossed over to ustekinumab treatment are presented in the placebo → 45 mg and placebo → 90 mg columns

Extracted from RE302:[S\_AE\_72\_H], 25JUN2007 9:49



#### 7.2.1.4 Deaths

One death was reported through the data cutoff for the BLA, a 33-year-old man (90 mg group) with a previously unrecognized idiopathic dilated cardiomyopathy who died from sudden cardiac death. The subject had received two administrations of 90 mg ustekinumab (Weeks 0 and 4) and died 5 days after his second administration or 5 weeks into the study. He had experienced a syncopal episode 9 weeks prior to randomization. Relevant past medical history included hypertension, hyperlipidemia, Graves disease, seizure disorder and a family medical history of early onset heart disease. Significant findings on autopsy included an enlarged, dilated heart (640 g) with no macroscopic or microscopic evidence of infarction, ischemia or myocarditis.

Based on Centers for Disease Control (CDC) estimates of expected rates of sudden cardiac death adjusted for age and gender, and all cause mortality in the US general population adjusted for age and gender, the rates of death in psoriasis clinical studies of ustekinumab were consistent with or lower than expected (standardized mortality ratio [SMR] = 0.78 [95% CI, 0.02, 4.33] for sudden cardiac death). For all causes of mortality, 8.11 deaths were expected through the data cutoff for the BLA and 1 death was observed (SMR = 0.12 [95% CI, 0.00, 0.69]; see Table 16).

**Table 16 Number of deaths through the data cutoff for the BLA in the psoriasis studies compared with the expected number of deaths from the general US population**

	Placebo	Ustekinumab
Subjects treated <sup>a</sup>	736	2301
Total subject-years of follow-up	184	1480
Observed number of deaths	0	1
Expected number of deaths <sup>b</sup>	1.06	8.11
SMR <sup>c</sup>	0.00	0.12
SMR 95% confidence interval <sup>d</sup>	(0.00, 2.82)	(0.00, 0.69)

<sup>a</sup> Psoriasis studies include T01, T02, T04, T08 (Week 52), and T09 (Week 28).

<sup>b</sup> The expected number of deaths adjusted for age and gender is based on Deaths: Preliminary Data for 2004, CDC National Vital Statistics Reports, vol 54 no 19, 2006.

<sup>c</sup> SMR = Standardized Mortality Ratio (observed number of deaths divided by expected number of deaths)

<sup>d</sup> Confidence intervals based on an exact method.

RE302:[S\_DTH\_11\_A], 03JUL2007 15:22

The Phase 3 studies are ongoing, and will continue for a total of 5 years. With continued follow-up, as of 05 May 2008, 3 additional deaths were reported in the ongoing studies of ustekinumab:

- A 63-year-old man (placebo crossover to 45 mg group) who had an unwitnessed death who was thought to have died from alcohol intoxication and aspiration based on autopsy and toxicology results approximately 1 week after his Week 44 visit and 4 weeks after his last administration of ustekinumab.
- A 43-year-old woman (90 mg group) who died during the long-term extension phase of the T09 study 10 days after her Week 60 visit. She died from massive post-operative intra-abdominal bleeding resulting in hemorrhagic shock, asystolic arrest, profound acidosis, and eventual multiorgan failure the day after undergoing an elective hysterectomy and an umbilical hernia repair.
- A 67-year-old man (placebo crossover to 90 mg group) who died during the long-term extension phase of T09, approximately 15 weeks after his Week 64 visit due to metastatic renal cancer. This subject presented with gross hematuria and was found on ultrasound to have a renal tumor with hepatic metastases. The lesions were never biopsied but the treating nephrologist suspected transitional cell carcinoma based on radiographic appearance.

One additional subject died of a drug overdose (methadone and sertraline) approximately 1 year after he completed the Phase 2 study.

No deaths have been reported in clinical studies of ustekinumab for other indications.

#### **7.2.1.5 Other Serious Adverse Events**

The proportions of subjects who had at least 1 SAE was 1.4 %, 1.6%, and 1.4% in the placebo, 45 mg, and 90 mg groups, respectively, through Week 12 (see Table 17). Most events occurred in only 1 subject in any treatment group, with the exception of cellulitis, which occurred in 2 (0.3%) subjects in the placebo group and 2 (0.3%) subjects in the 90 mg group, and intervertebral disc protrusion, which occurred in 2 (0.3%) subjects in the 45 mg group.

The 2 most frequently reported classes of SAEs were cardiac disorders and infections and infestations, both of which occurred in 0.3% of subjects in the combined ustekinumab group. SAEs in the cardiac system-organ class were reported in 0.0%, 0.1%, and 0.5% of subjects in the placebo, 45 mg, and 90 mg groups, respectively. SAEs in the infections and infestations system organ class were reported in 0.4%, 0.0%, and 0.5% of subjects in these respective groups. No consistent pattern of individual SAEs was observed. Further analyses of serious infections and cardiovascular events are presented in Sections 7.2.1.10.1.2 and 7.2.1.12, respectively.

**Table 17     Serious adverse events through Week 12 in Phase 2 and Phase 3**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated	732	790	792	1582
Avg duration of follow-up (weeks)	12.0	12.2	12.1	12.1
Avg exposure (weeks)	4.0	4.0	4.0	4.0
Subjects with 1 or more SAEs	10 (1.4%)	13 (1.6%)	11 (1.4%)	24 (1.5%)
System-organ class/preferred term				
Cardiac disorders	0 (0.0%)	1 (0.1%)	4 (0.5%)	5 (0.3%)
Acute myocardial infarction	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Angina pectoris	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Congestive cardiomyopathy	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Coronary artery disease	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Palpitations	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Ventricular extrasystoles	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Infections and infestations	3 (0.4%)	0 (0.0%)	4 (0.5%)	4 (0.3%)
Cellulitis	2 (0.3%)	0 (0.0%)	2 (0.3%)	2 (0.1%)
Herpes zoster	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Pneumonia	1 (0.1%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Injury, poisoning and procedural complications	0 (0.0%)	3 (0.4%)	0 (0.0%)	3 (0.2%)
Clavicle fracture	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Rib fracture	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Seroma	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Musculoskeletal and connective tissue disorders	1 (0.1%)	3 (0.4%)	0 (0.0%)	3 (0.2%)
Intervertebral disc protrusion	0 (0.0%)	2 (0.3%)	0 (0.0%)	2 (0.1%)
Dactylitis	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Psoriatic arthropathy	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	1 (0.1%)	2 (0.3%)	0 (0.0%)	2 (0.1%)
Cerebrovascular accident	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Sciatica	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Cervicobrachial syndrome	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Psychiatric disorders	1 (0.1%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
Alcohol withdrawal syndrome	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Psychotic disorder	1 (0.1%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Vascular disorders	0 (0.0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
Hypertension	0 (0.0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
Ear and labyrinth disorders	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Vertigo	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)

**Table 17** Serious adverse events through Week 12 in Phase 2 and Phase 3

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
General disorders and administration site conditions	1 (0.1%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Non-cardiac chest pain	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Chest pain	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Meningioma benign	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Hepatic neoplasm malignant	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Nephrolithiasis	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Skin and subcutaneous tissue disorders	1 (0.1%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Psoriasis	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Pityriasis rubra pilaris	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal disorders	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ascites	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asthma	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

RE302:[S\_SAE\_22\_1\_A], 25JUN2007 10:10

Most SAEs were considered serious because they resulted in hospitalization. Through the controlled portion, hospitalization rates per hundred subject-years of follow-up occurred at a rate of 5.17 (95% CI, 2.37, 9.82) in placebo-treated subjects compared with 7.46 (95% CI, 4.18, 12.31) in subjects in the 45 mg group and 5.95 (95% CI, 3.08, 10.40) in subjects in the 90 mg group.

To evaluate SAEs through the entire observation period (ie, through the data cutoff of the BLA), SAE rates per hundred subject-years of follow-up were evaluated. Serious adverse event rates were generally comparable between the placebo and the combined ustekinumab group (8.78 and 6.68 per hundred subject-years of follow-up, respectively). There were no SAEs that occurred in ustekinumab-treated subjects exceeding a rate of 1 per hundred subject-years of follow-up. Serious adverse events that occurred at a rate of at least 0.1 per hundred subject-years of follow-up in ustekinumab-treated subjects are shown in Table 18.

**Table 18**    **Serious adverse events reported at a rate of at least 0.1 per hundred subject-years of follow-up through the data cutoff for the BLA in Phase 2 and Phase 3**

	Placebo	Ustekinumab				
		Placebo → 45 mg <sup>a</sup>	Placebo → 90 mg <sup>a</sup>	45 mg	90 mg	Combined
Subjects treated	732	320	364	790	792	2266
Avg duration of follow-up (weeks)	12.9	26.4	25.2	37.0	37.2	33.7
Avg exposure (weeks)	4.9	17.1	15.0	26.5	26.6	23.4
Overall number of serious adverse events per hundred subject-years of follow-up	8.8	9.2	4.0	6.6	6.9	6.7
MedDRA system-organ class/preferred term						
Cardiac disorders						
Coronary artery disease	0.5	0.0	0.6	0.2	0.7	0.4
Myocardial infarction	0.5	0.0	0.6	0.2	0.2	0.2
Infections and infestations						
Cellulitis	1.1	0.0	0.0	0.2	0.5	0.3
Diverticulitis	0.0	0.0	0.0	0.0	0.4	0.1
Viral infection	0.0	0.0	0.0	0.2	0.2	0.1
Nervous system disorders						
Cerebrovascular accident	0.0	0.6	0.0	0.4	0.0	0.2
Psychiatric disorders						
Psychotic disorder	0.5	0.0	0.0	0.2	0.2	0.1
Musculoskeletal and connective tissue disorders						
Intervertebral disc protrusion	0.0	0.0	0.0	0.4	0.0	0.1
General disorders and administration site conditions						
Chest pain	0.5	0.6	0.0	0.0	0.2	0.1
Pregnancy, puerperium and perinatal conditions						
Abortion spontaneous	0.0	0.0	1.1	0.0	0.0	0.1
Vascular disorders						
Hypertension	0.0	0.0	0.0	0.2	0.2	0.1

<sup>a</sup> Placebo subjects who crossed over to ustekinumab treatment are presented in the placebo → 45 mg and placebo → 90 mg columns

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Rates of hospitalization per hundred subject-years of follow-up in ustekinumab-treated subjects remained stable or decreased slightly through the data cutoff for the BLA (4.85 [95% CI, 3.78, 6.12]) compared with the controlled period (6.71 [95% CI, 4.42, 9.76]).

### 7.2.1.6 Other Significant Adverse Events

#### 7.2.1.6.1 Adverse Events Leading to Discontinuation of Study Agent

The proportions of subjects who discontinued study agent because of an AE was low and comparable among treatment groups through Week 12 (1.9%, 1.1%, and 1.4% in the placebo, 45 mg, and 90 mg groups, respectively).

Treatment discontinuations due to AEs remained low through the data cutoff for the BLA (2.5% of subjects overall treated with ustekinumab).

#### 7.2.1.6.2 Injection-site Reactions

Ustekinumab injections were generally well tolerated. The proportions of subjects who had injection-site reactions to ustekinumab were low and comparable to the proportion of subjects who had an injection-site reaction to placebo (see Table 19). Approximately 1% of ustekinumab injections were complicated by an injection-site reaction, the majority of which were mild. One subject had a severe injection-site reaction of arm pain.

There was no apparent relationship between injection-site reactions and development of antibodies to ustekinumab.

**Table 19 Summary of injection-site reactions through the data cutoff for the BLA in Phase 2 and Phase 3**

	Placebo Injection	Ustekinumab		
		45 mg Injection	90 mg Injection	Combined
Treated subjects by study agent injection received	2304	1112	1158	2266
Avg number of injections	7.8	3.4	3.2	3.3
Subjects with 1 or more injection- site reactions	60 (2.6%)	30 (2.7%)	41 (3.5%)	71 (3.1%)
Total number of injections	17939	3768	3712	7480
Injections with injection-site reactions	76 (0.4%)	36 (1.0%)	49 (1.3%)	85 (1.1%)
Mild	73 (0.4%)	35 (0.9%)	48 (1.3%)	83 (1.1%)
Moderate	3 (< 0.1%)	1 (< 0.1%)	0 (0.0%)	1 (< 0.1%)
Severe	0 (0.0%)	0 (0.0%)	1 (< 0.1%)	1 (< 0.1%)

RE302:[S\_IR\_10\_A], 25JUN2007 10:08

**7.2.1.7 Possible Anaphylaxis or Serum Sickness-like Reactions**

No events of possible anaphylactic or serum sickness-like reaction to ustekinumab were reported.

**7.2.1.8 Adverse Events After Retreatment**

The safety of retreatment with ustekinumab was examined in the T04 and T08 studies.

- In T04, subjects with a PGA  $\geq 3$  at Week 16 were retreated with a single dose of ustekinumab at Week 16.
- In T08, subjects withdrawn from ustekinumab at Week 40 (PASI 75 responders at Weeks 28 and 40) were retreated with their original treatment regimen when they lost at least 50% of their PASI improvement achieved at Week 40.

The pattern of AEs after retreatment was generally comparable to that observed through the data cutoff for the BLA with the most frequently reported class of AEs occurring in the infections and infestations system-organ class (31.8% in the 45 mg group and 36.2% in the 90 mg group; see Table 20). No AEs of anaphylaxis or serum sickness-like reactions were reported.

**Table 20 Adverse events after retreatment reported with frequency of 2% or greater in ustekinumab-treated subjects; subjects retreated in T04 and T08**

	Ustekinumab		
	45 mg	90 mg	Combined
Retreated subjects	66	58	124
Avg duration of follow-up (weeks)	15.8	14.9	15.4
Subjects with 1 or more adverse events	38 (57.6%)	32 (55.2%)	70 (56.5%)
MedDRA System-organ class/preferred term			
Infections and infestations	21 (31.8%)	21 (36.2%)	42 (33.9%)
Nasopharyngitis	3 (4.5%)	6 (10.3%)	9 (7.3%)
Upper respiratory tract infection	4 (6.1%)	5 (8.6%)	9 (7.3%)
Urinary tract infection	4 (6.1%)	1 (1.7%)	5 (4.0%)
Cellulitis	3 (4.5%)	0 (0.0%)	3 (2.4%)
Influenza	1 (1.5%)	2 (3.4%)	3 (2.4%)
Otitis media	1 (1.5%)	2 (3.4%)	3 (2.4%)
Gastrointestinal disorders	6 (9.1%)	6 (10.3%)	12 (9.7%)
Diarrhoea	2 (3.0%)	1 (1.7%)	3 (2.4%)
Nausea	3 (4.5%)	0 (0.0%)	3 (2.4%)
Musculoskeletal and connective tissue disorders	10 (15.2%)	2 (3.4%)	12 (9.7%)
Back pain	3 (4.5%)	1 (1.7%)	4 (3.2%)
Arthralgia	3 (4.5%)	0 (0.0%)	3 (2.4%)
General disorders and administration site conditions	7 (10.6%)	3 (5.2%)	10 (8.1%)
Fatigue	2 (3.0%)	2 (3.4%)	4 (3.2%)
Nervous system disorders	5 (7.6%)	5 (8.6%)	10 (8.1%)
Headache	2 (3.0%)	4 (6.9%)	6 (4.8%)

Extracted from RE302:[S\_AE\_40\_1\_K], 25JUN2007 9:36

### 7.2.1.9 Laboratory Evaluations

Routine laboratory parameters were monitored throughout the observation period, including complete blood counts with white blood cell differential and platelet counts, and serum chemistries with electrolytes, liver, and kidney panels.

Markedly abnormal changes in hematology and chemistry laboratory values were generally infrequent, with comparable rates among the treatment groups through Week 12. Only decreased lymphocytes and elevated nonfasting glucoses occurred in



more than 1% of subjects, and rates were not higher in ustekinumab-treated subjects than in placebo-treated subjects. Through the data cutoff for the BLA, markedly abnormal changes in hematology and chemistry laboratory values remained comparable between the 45 mg and 90 mg groups, and rates of abnormalities did not increase disproportionately with increased duration of follow-up.

#### **7.2.1.10 Targeted Adverse Events**

Targeted analyses were conducted to evaluate events that represent theoretical risks of ustekinumab (serious infection [see Section 4.2.1], malignancy [see Section 4.2.1], asthma [see Section 4.3.3]) or that represent underlying risk in the psoriasis population (worsening psoriasis or psoriasis rebound, PsA, cardiovascular disease). When informative, safety event rates observed in clinical studies were compared with expected rates based on analyses of external databases.

Analyses of serious infection, malignancy, and cardiovascular events included comparisons between placebo- and ustekinumab-treated subjects during the controlled portions of:

- A 20-week placebo-controlled period from Phase 2 (T04);
- A 12-week placebo-controlled period from Phase 3 (T08 and T09).

##### **7.2.1.10.1 Infections**

Adverse events in the infections and infestations system-organ class were the most frequently reported class of AEs through Week 12, occurring in 23.0% of subjects in the placebo group, 26.6% in the 45 mg group, 25.1% in the 90 mg group (see Section 7.2.1.3). Most infections were self-limited, not serious, and did not require treatment discontinuation or interruption of treatment.

Rates of infections requiring antimicrobial treatment, serious infections, and infections of special interest based on the mechanism of action of ustekinumab (including TB and non-tuberculous mycobacterial diseases, salmonella, and opportunistic infections) were also examined.

##### **7.2.1.10.1.1 Infections Requiring Antimicrobial Treatment**

The number of subjects reporting at least 1 infection requiring oral or parenteral antimicrobial treatment through Week 12 was 7.7%, 7.3%, and 8.1% in the placebo, 45 mg, and 90 mg groups, respectively (see Table 21) for events occurring in at least 0.5% of ustekinumab-treated subjects. The most frequently reported infection requiring antimicrobial treatment in ustekinumab-treated subjects was upper respiratory tract infection, which was reported in comparable proportions of subjects in the placebo (1.1%), 45 mg (0.8%), and 90 mg (0.8%) groups.

**Table 21 Infections requiring oral or parenteral antimicrobial treatment through Week 12 in Phase 2 and Phase 3**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated	732	790	792	1582
Avg duration of follow-up (weeks)	12.0	12.2	12.1	12.1
Avg exposure (weeks)	4.0	4.0	4.0	4.0
Subjects with 1 or more infections requiring treatment	56 (7.7%)	58 (7.3%)	64 (8.1%)	122 (7.7%)
MedDRA System-organ class/preferred term				
Infections and infestations	52 (7.1%)	52 (6.6%)	58 (7.3%)	110 (7.0%)
Upper respiratory tract infection	8 (1.1%)	6 (0.8%)	6 (0.8%)	12 (0.8%)
Urinary tract infection	5 (0.7%)	4 (0.5%)	7 (0.9%)	11 (0.7%)
Sinusitis	9 (1.2%)	5 (0.6%)	5 (0.6%)	10 (0.6%)
Cellulitis	4 (0.5%)	4 (0.5%)	5 (0.6%)	9 (0.6%)
Bronchitis	6 (0.8%)	5 (0.6%)	3 (0.4%)	8 (0.5%)
Tooth infection	0 (0.0%)	5 (0.6%)	3 (0.4%)	8 (0.5%)

RE302:[S\_INFE\_18\_1\_A], 25JUN2007 10:04

**7.2.1.10.1.2 Serious Infections**

During the controlled portions of the studies, serious infections were reported at a rate of 1.70 (95% CI, 0.35, 4.96) per hundred subject-years of follow-up in placebo-treated subjects compared with 0.49 (95% CI, 0.01, 2.74) and 1.97 (95% CI, 0.54, 5.03) in subjects in the 45 mg and 90 mg ustekinumab groups, respectively (see Table 22). Cellulitis was the only serious infection reported in more than 1 subject in any treatment group, reported in 2 (0.3%) placebo-treated subjects and 2 (0.1%) ustekinumab-treated subjects.

**Table 22 Serious infections per hundred subject-years of follow-up during controlled portions of Phase 2 and Phase 3 psoriasis clinical studies**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated	732	790	792	1582
Total subject-years of follow-up	177	203	203	407
Number of serious infections	3	1	4	5
Event rate per 100 subject-years	1.70	0.49	1.97	1.23
95% confidence interval <sup>a</sup>	(0.35, 4.96)	(0.01, 2.74)	(0.54, 5.03)	(0.40, 2.87)

<sup>a</sup> Confidence intervals based on an exact method.

RE302:[S\_INFE\_14\_A], 25JUN2007 10:00

Overall rates of serious infections per hundred subject-years of follow-up in ustekinumab-treated subjects remained stable or decreased slightly through the data cutoff for the BLA (1.02 [95% CI, 0.57, 1.69]; see Table 23) compared with the controlled portions of the studies (1.23 [95% CI, 0.40, 2.87]). Serious infections reported in more than one subject included cellulitis (1 subject in the 45 mg group and 3 in the 90 mg group), diverticulitis (1 each in the 45 and 90 mg groups), and viral infection (1 each in the 45 and 90 mg groups).

**Table 23 Serious infections per hundred subject-years of follow-up in psoriasis Phase 2 and Phase 3 studies through the data cutoff for the BLA**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated <sup>a</sup>	732	1110	1156	2266
Total subject-years of follow-up	182	725	742	1467
Number of serious infections	3	6	9	15
Event rate per 100 subject-years	1.65	0.83	1.21	1.02
95% confidence interval <sup>b</sup>	(0.34, 4.81)	(0.30, 1.80)	(0.55, 2.30)	(0.57, 1.69)

<sup>a</sup> Placebo crossover subjects were included in ustekinumab columns after crossover to ustekinumab.

<sup>b</sup> Confidence intervals based on an exact method.

RE302:[S\_INFE\_14\_B], 25JUN2007 10:01

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Serious infections observed in the psoriasis clinical studies (including Phase 1) were compared to rates of infections requiring hospitalization observed in patients with psoriasis who were treated with systemic agents in the MarketScan Claims Database (adjusted for age and sex). These analyses showed that:

- Rates of serious infections in ustekinumab-treated subjects (1.01 per hundred subject-years of follow-up [95% CI: 0.57, 1.67]) were consistent with rates expected in psoriasis patients (1.49 per hundred subject-years of follow-up [95% CI: 0.93, 2.25]).

#### **7.2.1.10.1.3 Tuberculosis and Infections of Interest**

No cases of active TB were reported during the psoriasis Phase 2 and 3 studies. This included the 68 subjects who were randomized in the Phase 3 studies and received isoniazid for latent TB (ie, subjects with a positive purified protein derivative [PPD] test during screening, without evidence of TB on chest radiography). One additional subject with a negative PPD at screening developed latent TB after a TB exposure at work. He was subsequently treated with isoniazid during the study and did not develop active TB.

One subject in the 90 mg group had a potential opportunistic infection of possible disseminated, cutaneous herpes zoster; a 53-year-old woman with herpes zoster affecting the left T8 dermatome with 19 cutaneous vesicles disseminated beyond the primary dermatome but no identified visceral involvement, which resolved with antiviral therapy.

No other potential opportunistic infections were reported in any of the psoriasis studies.

No cases of non-tuberculous mycobacterial diseases, systemic fungal infections, or salmonellosis were reported.

#### **7.2.1.10.2 Malignancies**

During the placebo-controlled portions of the psoriasis clinical studies, malignancies were reported in 3 placebo-treated subjects and 4 ustekinumab-treated subjects (2 each in the 45 mg and 90 mg groups; see Table 24 for incidence rates). Three of the 4 malignancies reported in ustekinumab-treated subjects and 2 of the 3 malignancies reported in placebo-treated subjects were nonmelanoma skin cancers (NMSCs).

**Table 24 Malignancies during the controlled portions in Phase 2 and Phase 3 studies**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated	732	790	792	1582
Type of malignancy				
Nonmelanoma skin cancer				
Total subject-years of follow-up	176	203	203	406
Median subject-years of follow-up	0.2	0.2	0.2	0.2
Observed number of subjects	2	1	2	3
Incidence per 100 subject-years	1.13	0.49	0.98	0.74
95% confidence interval <sup>a</sup>	(0.14, 4.09)	(0.01, 2.75)	(0.12, 3.55)	(0.15, 2.16)
Malignancies other than nonmelanoma skin cancer				
Total subject-years of follow-up	177	203	203	406
Median subject-years of follow-up	0.2	0.2	0.2	0.2
Observed number of subjects	1	1	0	1
Incidence per 100 subject-years	0.57	0.49	0.00	0.25
95% confidence interval <sup>a</sup>	(0.01, 3.15)	(0.01, 2.75)	(0.00, 1.47)	(0.01, 1.37)
All malignancies				
Total subject-years of follow-up	176	203	203	406
Median subject-years of follow-up	0.2	0.2	0.2	0.2
Observed number of subjects	3	2	2	4
Incidence per 100 subject-years	1.70	0.99	0.98	0.99
95% confidence interval <sup>a</sup>	(0.35, 4.98)	(0.12, 3.57)	(0.12, 3.55)	(0.27, 2.52)

<sup>a</sup> Confidence intervals based on an exact method assuming that the observed number of subjects with events follows a Poisson distribution.

RE333:[S\_MAL\_27\_A], 29JAN2008 14:29

Through the data cutoff for the BLA, a total of 19 ustekinumab-treated subjects reported a malignancy, 14 with NMSC and 5 with solid tumor malignancies including 2 subjects

with prostate cancer and 1 subject each with breast, transitional cell kidney, and thyroid cancer. Overall rates of malignancies per hundred subject-years of follow-up in ustekinumab-treated subjects were generally comparable between the controlled portions of the studies (0.99 [95% CI, 0.27, 2.52]) and through the data cutoff for the BLA (1.30 [95% CI, 0.78, 2.03]).

The rates of noncutaneous malignancies observed through the data cutoff for the BLA were compared with rates expected in US population adjusted for age, gender, and race based on data available in the National Institutes of Health SEER ([Surveillance, Epidemiology, and End Results](#)) database (2004). The standardized incidence ratio (SIR) was 0.71 (95% CI: 0.23, 1.65) for ustekinumab-treated subjects and 1.12 (95% CI: 0.03, 6.24) for placebo-treated subjects (see Table 25).

**Table 25 Noncutaneous solid tumor malignancies in Phase 2 and Phase 3 studies compared with the expected number in the general US population according to the SEER database**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated <sup>a</sup>	732	1110	1156	2266
Total subject-years of follow-up	182	723	742	1466
Median subject-years of follow-up	0.2	0.5	0.5	0.5
Observed number of subjects <sup>b</sup>	1	5	0	5
Expected number of subjects <sup>c</sup>	0.89	3.45	3.61	7.05
SIR <sup>d</sup>	1.12	1.45	0.00	0.71
SIR 95% confidence interval <sup>e</sup>	(0.03, 6.24)	(0.47, 3.39)	(0.00, 0.83)	(0.23, 1.65)

<sup>a</sup> Placebo crossover subjects were included in ustekinumab columns after crossover to ustekinumab.

<sup>b</sup> All malignancies other than nonmelanoma skin cancers.

<sup>c</sup> The expected number of subjects with malignancies is based on the [SEER Database \(2004\)](#), adjusted for age, gender, and race.

<sup>d</sup> SIR = Standardized Incidence Ratio (observed number of subjects with malignancy divided by expected number of subjects with malignancy)

<sup>e</sup> Confidence intervals based on an exact method.

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The rates of NMSCs observed through the data cutoff for the BLA were compared with rates reported in subjects treated with 3 biologics approved for the treatment of psoriasis (see Table 26). These were considered appropriate comparisons because any ascertainment bias that might result from unmasking NMSCs that were previously concealed by psoriatic plaques would be expected to be generally similar with other psoriasis treatments. The generally comparable incidence in ustekinumab-treated subjects and subjects treated with each of these 3 biologic treatments (with a similar patient population) suggests that ustekinumab does not increase rates of NMSC compared

with other currently approved biological agents, though it cannot be concluded from these analyses that treatment with biologics does not impact NMSC incidence.

**Table 26 Summary of nonmelanoma skin cancer rates of ustekinumab, infliximab, efalizumab, and etanercept in psoriasis clinical studies**

	Ustekinumab <sup>a</sup>	Infliximab <sup>a</sup>	Efalizumab <sup>b</sup>	Etanercept <sup>c</sup>
Total subject-years of follow-up <sup>d</sup>	1463	1101	1784	1062
Number of subjects with events	14	17	20	12
Incidence per 100 subject-years	0.96	1.54	1.12	1.13
95% confidence interval <sup>e</sup>	(0.52, 1.61)	(0.90, 2.47)	(0.68, 1.73)	(0.58, 1.97)

<sup>a</sup> Includes data from Phase 2 and Phase 3.

<sup>b</sup> Data are from dermatologic and ophthalmic drugs advisory committee meeting, 9 September 2003, RAPTIVA™ (efalizumab).

<sup>c</sup> Data are from Enbrel label approved on 27 September 2004, BLA 103795.

<sup>d</sup> NMSC includes basal and squamous cell skin cancers.

<sup>e</sup> Confidence intervals based on an exact method.

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Other comparator databases (eg, the MarketScan Claims Database) were not used to determine expected rates because ascertainment bias limits interpretability of such comparisons. Many patients in such databases may not be followed by a dermatologist and NMSC may go unrecognized by non-dermatologists.

#### **7.2.1.10.2.1 Characteristics of Malignancies Observed in Psoriasis Clinical Studies**

The malignancies observed in the psoriasis clinical studies did not reveal a pattern that was suggestive of immunosuppression. In particular, the noncutaneous malignancies were common types of malignancies in the general population (prostate, breast, kidney, thyroid) of varied histogenesis not suggesting a common mechanistic link, and no lymphomas were reported, for which patients with psoriasis are reportedly at higher risk (Gelfand et al, 2006b).

A total of 21 NMSCs were reported in 14 subjects. Four subjects had multiple NMSC.

Overall, the ratio of subjects with basal:squamous cell cancers in the psoriasis clinical studies was 4:1, which is consistent with the ratio observed in immunocompetent patients in the general population (4:1), and does not reflect the reversal of this ratio seen in immunosuppressed patients (eg, with immunosuppression post-organ transplant [Rubin et al, 2005]).

Overall, the types of malignancies observed do not reveal a pattern that is suggestive of immunosuppression.

#### **7.2.1.11 Asthma**

Approximately 8% of subjects in the Phase 3 studies reported a medical history of asthma (see Table 13). Through the data cutoff for the BLA, no SAEs of asthma or treatment discontinuations due to asthma were reported in ustekinumab-treated subjects. One SAE of asthma exacerbation was reported in a placebo-subject. Adverse events of asthma were infrequent (0.3% in ustekinumab-treated subjects and 0.1% in placebo-treated subjects through Week 12), responded appropriately to therapy, and showed no clear relationship to drug exposure.

A total of 450 (22.5%) subjects enrolled in Phase 3 studies reported a medical history of seasonal allergies, and 23 (1.2%) of subjects reported atopic dermatitis, which may represent Th2-mediated conditions. Adverse events of seasonal allergy were uncommon, reported in 3 (0.2%) ustekinumab-treated subjects through 12 weeks of treatment, and a single AE of atopic dermatitis was reported in a subject who received placebo.

Combined, these observations do not suggest a detrimental effect of ustekinumab on asthma or other atopic or Th2-mediated diseases.

#### **7.2.1.12 Cardiovascular Events**

Cardiovascular events in clinical studies of ustekinumab were evaluated because the target patient population is known to be at increased risk of cardiovascular morbidity, and background rates of cardiovascular risk factors were high in the Phase 2 and 3 population (see Section 7.2.1.2). Approximately two-thirds of subjects in the Phase 3 studies had at least 2 cardiovascular risk factors as defined by the National Cholesterol Education Program (NCEP, 2002), and one-third had at least 3 risk factors. A total of 69% of subjects had a low high-density lipoprotein (HDL; < 40 mg/dL), approximately half were obese, and 40% met modified NCEP criteria for Metabolic Syndrome.

Additionally, a numeric imbalance in serious cardiovascular AEs was observed in the Phase 2 study with a 4:1 ustekinumab to placebo randomization (3 events of MI or stroke, in the ustekinumab-treated subjects versus none in the placebo-treated subjects]). Therefore, cardiovascular events were further evaluated in Phase 3 using the following analytical approaches:

- As a primary approach, a composite of major adverse cardiovascular events (cardiovascular death, MI and stroke) was analyzed.
- Since the events observed in Phase 2 were thrombotic in nature, additional analyses evaluated a broader group of SAE terms using International Classification of Disease (ICD) 9 codes for all ischemic cardiovascular and cerebrovascular events



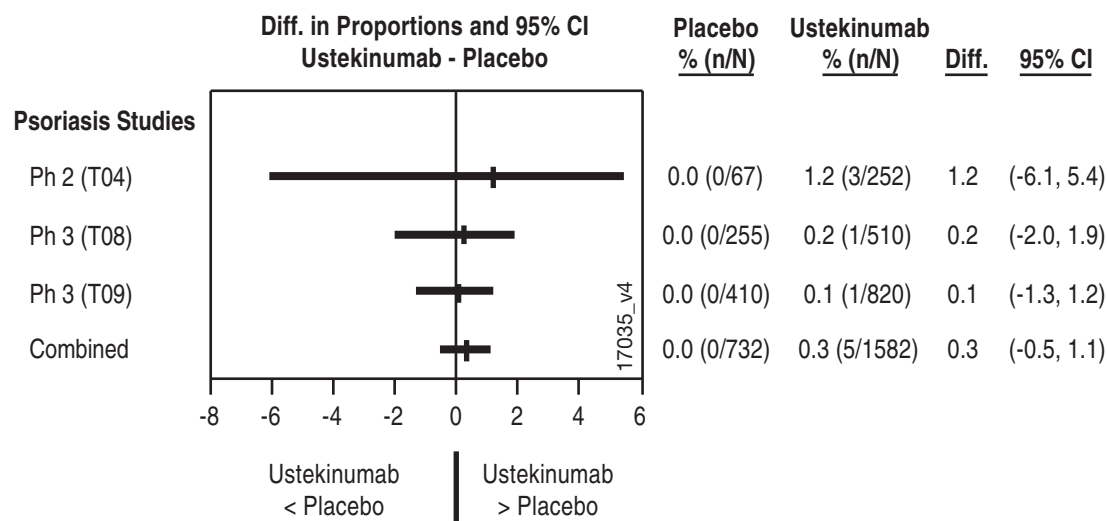
which were mapped to corresponding MedDRA terms. This composite includes MI, stroke, angina [stable or unstable] and transient ischemic attacks.

- Comparisons of event rates in the psoriasis program were made to established external databases and to publicly available data from other approved biologic agents.

#### 7.2.1.12.1 Cardiovascular Events in Phase 2 and Phase 3

The numeric imbalance in major adverse cardiovascular events observed in Phase 2 was attenuated in the larger Phase 3 studies with a single event observed in each study (T08 and T09). Figure 18 illustrates risk differences observed between ustekinumab- and placebo-treated subjects by study and for data combined from the Phase 2 and Phase 3 psoriasis studies. The confidence intervals around the point estimates overlap 0 for each study as well as in the combined Phase 2 and Phase 3 data. Relative risks could not be calculated because of the absence of events in the placebo group.

Post-hoc, independent, blinded adjudication of a broad range of SAE terms potentially coding to both cardiovascular and cerebrovascular events performed by the Cleveland Clinic Coordinating Center for Clinical Research (C5) confirmed the diagnosis of each major adverse cardiovascular event and did not alter these results. All these subjects had at least 2 established cardiovascular risk factors.



**Figure 18 Risk difference (excess risk) in major adverse cardiovascular events (cardiovascular death, MI and stroke) in individual studies and pooled Phase 2 and Phase 3 studies**

### 7.2.1.12.2 Serious Cardiovascular Events During the Controlled Period

Analyses of rates of major adverse cardiovascular events adjusted for follow-up using data pooled from the Phase 2 and Phase 3 studies are shown in Table 27. Additional analyses of serious ischemic cardiovascular and cerebrovascular events showed that no events were observed in the placebo group, and a total of 6 events were reported in ustekinumab-treated subjects: 3 (1.48/100 subject years) subjects in the 45 mg group and 3 (1.47/100 subject years) subjects in the 90 mg group (see Table 27). Three of these events in each of these analyses occurred in the Phase 2 study.

**Table 27 Major adverse cardiovascular events and serious ischemic cardiovascular events and cerebrovascular events during controlled portions of pooled psoriasis Phase 2 and Phase 3 studies**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated	732	790	792	1582
Total subject-years of follow-up	177	203	203	407
Median subject-years of follow-up	0.2	0.2	0.2	0.2
Type of events				
Major adverse cardiovascular events <sup>a</sup>				
Observed number of events	0	2	3	5
Event rate per 100 subject-years	0.00	0.98	1.47	1.23
95% confidence interval <sup>b</sup>	(0.00, 1.69)	(0.12, 3.56)	(0.30, 4.31)	(0.40, 2.87)
Serious ischemic cardiovascular and cerebrovascular events <sup>c</sup>				
Observed number of events	0	3	3	6
Event rate per 100 subject-years	0.00	1.48	1.47	1.48
95% confidence interval <sup>b</sup>	(0.00, 1.69)	(0.30, 4.31)	(0.30, 4.31)	(0.54, 3.21)

<sup>a</sup> Major adverse cardiovascular events = sudden cardiac death, MI, or stroke

<sup>b</sup> Confidence intervals based on an exact method.

<sup>c</sup> Serious ischemic cardiovascular and cerebrovascular events were based on broad mapping of ICD-9 codes for ischemic cardiovascular and cerebrovascular diseases to MedDRA terms

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### **7.2.1.12.3 Sensitivity Analyses**

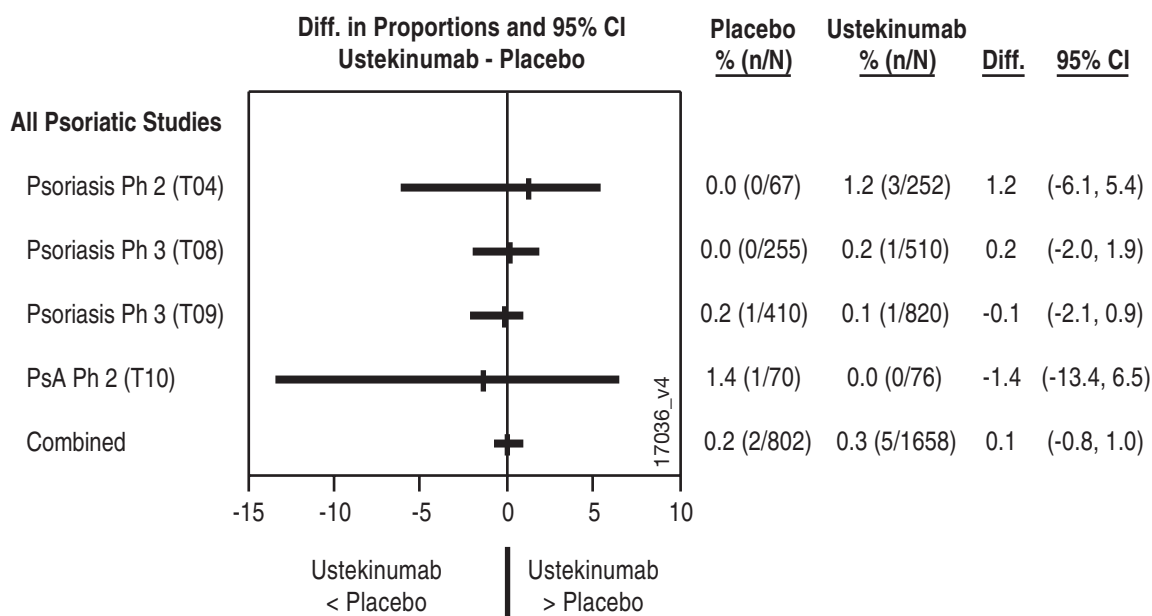
#### **Sensitivity Analysis of Major Adverse Cardiovascular Events**

A sensitivity analysis of major adverse cardiovascular events was performed that included:

- Data from a concurrently conducted Phase 2 study in psoriatic arthritis (T10) because both populations have similar baseline characteristics and cardiovascular risk factors;
- All data in subjects treated only with placebo. (Note that subjects who discontinued study agent in Phase 3 were followed for approximately 20 weeks after their last dose of study agent. Therefore, placebo-randomized subjects who discontinued study agent prior to Week 12 have additional follow-up beyond the placebo-controlled period).

In this post-hoc sensitivity analysis, the combined estimate of risk difference was attenuated highlighting the fragility of the point estimate during the placebo-controlled period (see Figure 19).

This resulted from two additional major adverse cardiovascular events in placebo-treated subjects and none in ustekinumab-treated subjects. One MI occurred in the placebo group in the T10 study in a subject with moderate to severe psoriasis. The other MI occurred in a 59-year-old female in the T09 study who had an MI 3 days after the Week 12 visit and thus this event is not included in the primary analysis. This subject never received ustekinumab because she discontinued study agent prior to placebo crossover (ie, prior to Week 12) due to a serious adverse event of PsA, but was in routine follow-up.



**Figure 19 Risk difference (excess risk) in major adverse cardiovascular events (cardiovascular death, MI and stroke) in clinical studies of psoriatic diseases (psoriasis and PsA Phase 2 and Phase 3 clinical studies)**

### **Serious and Nonserious Cardiovascular Events in Phase 2 and 3 Psoriasis Studies**

Sensitivity analysis that evaluated all serious and nonserious cardiovascular AEs combined through Week 12 did not reveal any imbalance between the placebo and ustekinumab groups. Specifically, 4.5% of placebo-treated subjects experienced a nonserious or serious cardiovascular AEs compared with 3.8% and 4.3% of subjects in the 45 mg and 90 mg ustekinumab treatment groups, respectively. No pattern of events with common pathophysiology (eg, heart failure, arrhythmia, ischemia) was observed suggesting an association with ustekinumab.

#### **7.2.1.12.4 Serious Cardiovascular Events Through the Data Cutoff for the BLA**

Through the data cutoff for the BLA, rates of major adverse cardiovascular events per hundred subject-years of follow-up remained generally stable or decreased (eg, major adverse cardiovascular events of 0.61 [95% CI, 0.28, 1.16] compared with 1.23 [95% CI, 0.40, 2.87] during the shorter controlled portions of the studies). Of note, the event of MI in the T09 subject who had an MI 3 days after Week 12, while not seen in the primary placebo-controlled period analysis (see Table 27), is seen in the analysis through the data cutoff for the BLA (see Table 28). A similar pattern was seen with the broader cardiovascular composite.

**Table 28 Major adverse cardiovascular events and serious ischemic cardiovascular events and cerebrovascular events through the data cutoff for the BLA in psoriasis Phase 2 and Phase 3 studies**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated <sup>a</sup>	732	1110	1156	2266
Total subject-years of follow-up	182	725	742	1467
Median subject-years of follow-up	0.2	0.5	0.5	0.5
Type of events				
Major adverse cardiovascular events <sup>b</sup>				
Observed number of events	1	5	4	9
Event rate per 100 subject-years	0.55	0.69	0.54	0.61
95% confidence interval <sup>c</sup>	(0.01, 3.06)	(0.22, 1.61)	(0.15, 1.38)	(0.28, 1.16)
Serious ischemic cardiovascular events and cerebrovascular events <sup>d</sup>				
Observed number of events	1	7	7	14
Event rate per 100 subject-years	0.55	0.97	0.94	0.95
95% confidence interval <sup>c</sup>	(0.01, 3.06)	(0.39, 1.99)	(0.38, 1.94)	(0.52, 1.60)

<sup>a</sup> Placebo crossover subjects are included in ustekinumab columns after crossover to ustekinumab.

<sup>b</sup> Major adverse cardiovascular events = sudden cardiac death, MI, or stroke

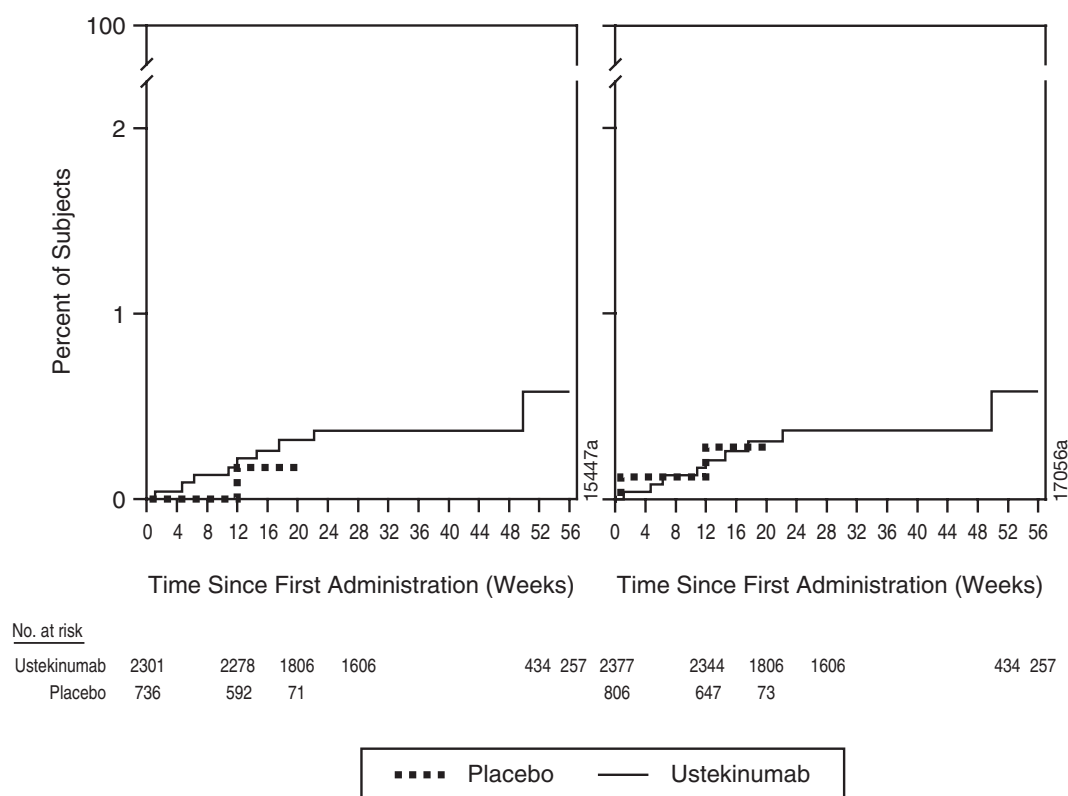
<sup>c</sup> Confidence intervals based on an exact method.

<sup>d</sup> Serious ischemic cardiovascular and cerebrovascular events were based on broad mapping of ICD-9 codes for ischemic cardiovascular and cerebrovascular diseases to MedDRA terms

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#### 7.2.1.12.5 Serious Cardiovascular Events Over Time

Time to first event (Kaplan-Meier) analyses were conducted to evaluate rates of major adverse cardiovascular events over time all psoriasis studies including Phase 1 (see Figure 20, left side) and across all psoriatic studies (see Figure 20, right side). Event rates over time were low (< 1%) in all groups, and no evidence of an increase over time was observed in ustekinumab-treated subjects. The low event rate and comparatively smaller numbers of subjects in the placebo groups limits interpretability of the curves, though a separation of the curves is not apparent for either the psoriasis studies (left) or for all studies in psoriatic diseases (right).



**Figure 20 Time to first major adverse cardiovascular event analysis for psoriasis studies (left) and all psoriatic studies (right) through the data cutoff for the BLA**

#### 7.2.1.12.6 Comparisons of Serious Cardiovascular Events with External Data

Using a predictive model developed from the Framingham Heart Study, rates of major adverse cardiovascular events in the psoriasis clinical study program were compared to rates expected in the general population after adjustment for demographics and underlying cardiovascular risk factors including total cholesterol, HDL cholesterol, blood pressure, diabetes, and smoking history. Overall rates of MIs and strokes were consistent with rates expected given the risk factor distribution (standardized incidence ratio 0.87 [95% CI, 0.38, 1.72]; see Table 29).

**Table 29 Rates of myocardial infarctions or strokes through the data cutoff for the BLA in psoriasis Phase 2 and Phase 3 studies compared with the number expected in the general US population based on the Framingham Heart Study**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated <sup>a</sup>	732	1110	1156	2266
Type of events				
Myocardial infarction or stroke				
Subject-years of follow-up	182	723	741	1463
Events observed	1	5	3	8
Expected number of events <sup>b</sup>	1.04	4.48	4.68	9.16
SIR <sup>c</sup>	0.96	1.12	0.64	0.87
SIR 95% confidence interval <sup>d</sup>	(0.02, 5.35)	(0.36, 2.60)	(0.13, 1.87)	(0.38, 1.72)

<sup>a</sup> Psoriasis studies include Phase 2 T04 and Phase 3 (T08 [Week 52], and T09 [Week 28]). Placebo crossover subjects are included in ustekinumab columns after crossover to ustekinumab.

<sup>b</sup> The expected number of serious cardiovascular events in the general US population is calculated based on a prediction model (Weibull) from the Framingham Heart Study, adjusted for selected baseline demographics and co-morbidities.

<sup>c</sup> SIR = Standardized Incidence Ratio (observed number of subjects with serious cardiovascular events divided by expected number of subjects with serious cardiovascular events predicted from the Framingham study)

<sup>d</sup> Confidence intervals based on an exact method assuming that the observed number of subjects with events follows a Poisson distribution.

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Event rate comparisons to data from other external sources showed similar results and are summarized below:

- Rates of serious ischemic cardiovascular and cerebrovascular events were consistent with rates expected in the general US population utilizing the CDC database (rate ratio 0.94 [95% CI, 0.51, 1.57]).
- Rates of MIs and strokes were consistent with or lower than rates predicted by models developed using psoriasis specific populations from the United Kingdom General Practice Research Database (GPRD) after adjustment for both demographic and underlying cardiovascular risk factors (SIR 0.53 [95% CI, 0.23, 1.04]).

- Rates of major adverse cardiovascular events (cardiovascular death, MI and stroke) were consistent with rates in psoriasis clinical studies of other approved biologic agents. Rates were obtained from integrated summary of safety for both ustekinumab and infliximab, and from the FDA summary basis of approvals and/or briefing documents for etanercept, alefacept and efalizumab. Rates per 100 subject years of exposure for major adverse cardiovascular events in psoriasis BLAs or sBLAs were: 0.61 for ustekinumab, 0.36 for infliximab, 0.76 for etanercept, 0.62 in alefacept and 0.25 for efalizumab.

#### **7.2.1.12.7 Cardiovascular Risk Factors and Biomarkers**

To further evaluate whether ustekinumab impacts cardiovascular risk, analyses of several risk factors or biomarkers were conducted over the controlled period of the Phase 3 studies. As expected based on mechanism of action, mean C-reactive protein levels decreased slightly more in the ustekinumab groups compared with the placebo group. No impact of ustekinumab was observed on blood pressure, body weight, fasting glucose, glycosylated hemoglobin (Hb A1C), or D-dimer (as a measure of occult thrombosis).

Post-hoc analyses of lipids in the T08 and T09 studies showed that ustekinumab-treated subjects had slightly greater increases in fasting total cholesterol (TC), low-density lipoprotein cholesterol, HDL cholesterol, and triglycerides without a significant change in TC/HDL ratios. Combined, these analyses do not suggest a mechanistic basis by which ustekinumab increases cardiovascular risk.

#### **7.2.1.13 Adverse Events of Psoriasis**

The rate of psoriasis AEs was low in the Phase 2 and 3 studies. Through Week 12, AEs of psoriasis occurred in 2.3% of placebo-treated subjects compared with 0.4% and 1.4% of subjects in the 45 mg and 90 mg ustekinumab treatment group, respectively (see Table 30).



**Table 30 Adverse events of psoriasis through Week 12 in Phase 2 and Phase 3**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated	732	790	792	1582
Subjects with 1 or more adverse events of psoriasis	17 (2.3%)	3 (0.4%)	11 (1.4%)	14 (0.9%)
Lower level term category				
Erythrodermic psoriasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pustular psoriasis	1 (0.1%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Guttate psoriasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Worsening or exacerbation of psoriasis	16 (2.2%)	3 (0.4%)	10 (1.3%)	13 (0.8%)
Inverse psoriasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Palmo-plantar psoriasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Placebo subjects who had AEs of psoriasis did so throughout the placebo period, while most AEs in ustekinumab-treated subjects occurred early in the treatment course, often within the first week, with subsequent response to treatment. This pattern presumably represents the lag prior to reaching drug concentrations that may be therapeutic. Through the end of study, AE rates remained low, 1.3% in the combined treatment group.

One ustekinumab-treated subject had an SAE of psoriasis:

- The subject's (90 mg group) disease worsened during the screening period (PASI score increased from 13.2 at screening to 22.3 at baseline, prior to the administration of study agent). The subject was hospitalized on Day 8, treated with emollients only, and subsequently continued in the study, becoming a PASI 75 responder at Week 12 and clearing completely by Week 20.

Rebound is defined as a PASI of 125% of baseline, of new generalized pustular, erythrodermic or more inflammatory psoriasis occurring within 3 months of stopping therapy ([Gordon et al, 2005](#)). Rebound is best evaluated in T08, where the recommended dosage regimen was used and treatment was discontinued in the randomized withdrawal period where long-term PASI 75 responders (subjects who were responders at Weeks 28 and 40 to ustekinumab) were withdrawn from therapy. No subjects in the withdrawal group reported an AE of erythrodermic or pustular psoriasis. Subjects withdrawn from ustekinumab did not experience rebound through Week 40, because they were responders during that treatment phase. Further, no subject who was withdrawn from therapy at

Week 40 (ie, received their last injection at Week 28) met the definition of rebound when followed for up to 180 days after the last ustekinumab administration.

#### **7.2.1.14 Adverse Events of Psoriatic Arthritis**

Approximately one-quarter to one-third of subjects in T08 and T09 reported PsA as a baseline comorbidity.

In the placebo-controlled portion of the studies, psoriatic arthropathy occurred in 1.6% of placebo subjects compared with 0.6% of combined ustekinumab subjects and arthritis occurred in 0.7% of subjects in the placebo group compared with 0.5% of subjects in the combined ustekinumab group. Through the data cutoff for the BLA, AEs of psoriatic arthropathy occurred in 1.0% and arthritis occurring in 0.8% of ustekinumab-treated subjects.

A Phase 2 study of ustekinumab in PsA demonstrated that 4 weekly SC doses of ustekinumab was effective in treating PsA when compared with placebo.

Combined, these observations do not suggest that ustekinumab exacerbated or worsened PsA.

#### **7.2.1.15 Special Consideration Per Target Population**

##### **7.2.1.15.1 Impact of Weight on Safety**

The impact of weight on the safety was examined by evaluating rates of AEs, SAEs, and AEs leading to study agent discontinuation in subjects weighing  $\leq 100$  kg or  $> 100$  kg, as well as in subpopulations defined by 10 kg increments of body weight. During the placebo-controlled period, rates of AEs, SAEs, and AEs leading to study agent discontinuation were generally comparable between groups within each subpopulation analyzed, and similar patterns of AEs were observed in subjects weighing  $\leq 100$  kg or  $> 100$  kg (see Table 31). Through the data cutoff for the BLA, rates of AEs, SAEs, and AEs leading to study agent discontinuation were generally comparable between subjects in the 45 mg and 90 mg groups.

**Table 31 Adverse events, serious adverse events, and adverse events leading to discontinuation by body weight ( $\leq 100$  kg,  $> 100$  kg) through Week 12 in Phase 2 and Phase 3**

	Placebo	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated	732	790	792	1582
Subjects with weight $\leq 100$ kg				
n	502	556	542	1098
Avg duration of follow-up (weeks)	12.0	12.2	12.1	12.2
Subjects with 1 or more adverse events	255 (50.8%)	323 (58.1%)	278 (51.3%)	601 (54.7%)
Subjects with 1 or more serious adverse events	8 (1.6%)	8 (1.4%)	5 (0.9%)	13 (1.2%)
Subjects who discontinued study because of 1 or more adverse events	8 (1.6%)	5 (0.9%)	8 (1.5%)	13 (1.2%)
Subjects with weight $> 100$ kg				
n	230	234	249	483
Avg duration of follow-up (weeks)	12.0	12.1	12.1	12.1
Subjects with 1 or more adverse events	114 (49.6%)	132 (56.4%)	131 (52.6%)	263 (54.5%)
Subjects with 1 or more serious adverse events	2 (0.9%)	5 (2.1%)	6 (2.4%)	11 (2.3%)
Subjects who discontinued study because of 1 or more adverse events	6 (2.6%)	4 (1.7%)	3 (1.2%)	7 (1.4%)

RE302:[S\_AE\_18\_A], 17JUL2007 15:44

#### 7.2.1.15.2 Safety with Long-term Continuous Use (Randomized Withdrawal)

The safety of long-term continuous maintenance dosing was examined by evaluating rates of AEs, SAEs, and AEs leading to study agent discontinuation among subjects randomized at Week 40 (randomized withdrawal analysis). During this controlled period, rates of AEs, SAEs, and AEs leading to study agent discontinuation were generally comparable between subjects who received continuous maintenance dosing and those who received placebo (see Table 32), and the pattern of AEs observed in this study period was generally comparable to that observed in other study periods.

**Table 32 Adverse events, serious adverse events, and adverse events leading to discontinuation in subjects during the randomized withdrawal portion of T08**

	Ustekinumab		
	Combined		
	Placebo	Placebo → Retreatment	q12 wks
Subjects randomized at Week 40 and subsequently treated	160	17	161
Avg duration of follow-up (weeks)	14.8	6.8	15.6
Avg exposure (weeks)	10.9	2.8	11.7
Subjects with 1 or more adverse events	83 (51.9%)	4 (23.5%)	76 (47.2%)
Subjects with 1 or more serious adverse events	2 (1.3%)	0 (0.0%)	1 (0.6%)
Subjects who discontinued study agent because of 1 or more adverse events	2 (1.3%)	0 (0.0%)	3 (1.9%)

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### 7.2.1.15.3 Safety With Self-administration

Subjects in the Phase 3 studies were encouraged to self-administer study agent beginning at Week 12. In the T08 study, ustekinumab safety was compared in subjects who self-administered drug versus those in whom drug was administered by a health care professional during the randomized withdrawal portion of the study. The proportions of subjects with AEs, SAEs, infections, or AEs leading to study agent discontinuation were generally comparable in subjects who self-administered ustekinumab and in the population of subjects in whom ustekinumab was administered by a health care professional (see Table 33). Similarly, in T09, the proportions of subjects with AEs, SAEs, infections, or AEs leading to study agent discontinuation between Weeks 16 to 28 was comparable with self-administration and administration by a health care professional. Moreover, similar rates were also observed with ustekinumab-treated and placebo-treated subjects.

**Table 33 Adverse events, serious adverse events, infections, or adverse events leading to discontinuation with self versus health care professional administration of study agent during the randomized withdrawal portion of T08**

	Ustekinumab			
	Self Administered		Health Care Professional Administered	
	Placebo	q12 wks	Placebo	q12 wks
Subjects randomized at Week 40 and subsequently treated <sup>a</sup>	93	95	66	66
Avg duration of follow-up (weeks)	15.2	15.9	14.4	15.2
Avg exposure (weeks)	11.3	12.0	10.4	11.3
Subjects with 1 or more adverse events	51 (54.8%)	45 (47.4%)	31 (47.0%)	31 (47.0%)
Subjects with 1 or more serious adverse events	1 (1.1%)	0 (0.0%)	1 (1.5%)	1 (1.5%)
Subjects with 1 or more infections	32 (34.4%)	29 (30.5%)	24 (36.4%)	23 (34.8%)
Subjects who discontinued study agent because of 1 or more adverse events	0 (0.0%)	0 (0.0%)	2 (3.0%)	3 (4.5%)

<sup>a</sup> Subjects were considered "Self Administered" if at least one injection at Week 40 was self administered. Otherwise, they were considered "Health Care Professional Administered" if at least 1 injection at Week 40 was administered by a health care professional.

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Rates and severity of injection-site reactions were also similar regardless of whether ustekinumab was self-administered or administered by a health care professional. Combined, these results suggest that the safety of ustekinumab is similar regardless of whether the product is self-administered or administered by a health care professional.

**Table 34 Summary of injection-site reactions through the date the last subject completed Week 52 in T08 with self versus health care professional administration**

	Self Administered		Health Care Professional Administered	
	Placebo	Ustekinumab	Placebo	Ustekinumab
Treated subjects by self vs health care professional administration and study agent injection received	524	454	765	728
Avg number of injections	8.2	2.4	8.0	3.3
Subjects with 1 or more injection-site reactions	4 (0.8%)	12 (2.6%)	22 (2.9%)	16 (2.2%)
Total number of injections	4273	1111	6144	2399
Injections with injection-site reactions	5 (0.1%)	14 (1.3%)	27 (0.4%)	18 (0.8%)
Mild	5 (0.1%)	14 (1.3%)	24 (0.4%)	18 (0.8%)
Moderate	0 (0.0%)	0 (0.0%)	3 (0.0%)	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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## 7.2.1.16 Special Safety Topics Unique to Drug

### 7.2.1.16.1 Pregnancy

The effects of ustekinumab during pregnancy are not known. Nonclinical studies have shown no adverse effect. Toxicokinetic analyses confirmed high maternal exposure to ustekinumab and also demonstrated fetal exposure to ustekinumab at the time of C-section indicating that ustekinumab crossed the placenta.

During the clinical studies of ustekinumab, a total of 30 prospective cases of pregnancy were identified across all clinical studies of ustekinumab (protocol deviations). Of these, 13 were recognized as maternal pregnancy cases and 17 were the result of paternal exposure. Study agent was discontinued in all pregnant women, so embryonic/fetal exposure to ustekinumab is expected to be limited. Prospective maternal pregnancy outcomes by study are presented in Table 35.

**Table 35 Summary of pregnancies in ustekinumab clinical studies**

Outcome	Indication			Total
	Psoriasis	MS	PsA	
Live birth with no defect or other AE	1	1	0	2 <sup>a</sup>
Spontaneous abortion	1	0	0	1
Elective termination	5	0	0	5
Fetal deaths	0	0	0	0
Live births with defect	0	0	0	0
Live births with other AE	0	0	0	0
Unknown outcome <sup>b</sup>	4	0	1	5
<b>TOTAL</b>	<b>11</b>	<b>1</b>	<b>1</b>	<b>13</b>

<sup>a</sup> Both female

<sup>b</sup> 3/5 pregnancies were currently ongoing at the time of analysis; 2 pregnancies had an unknown outcome

Note: Events in this table are from Johnson & Johnson Benefit Risk Management worldwide safety database through 16 Jul 2007 (SAE data cutoff for the BLA).

*Spontaneous Abortion:* One case of spontaneous abortion was reported in a 42-year-old female treated with ustekinumab for severe plaque psoriasis. No fetal heartbeat was detected on exam at approximately 12 weeks of gestation. An echography/ultrasound confirmed fetal demise. Concomitant medications included hydrochlorothiazide, hydroxyzine hydrochloride and Tylenol #3. Past medical history included prior elective abortion, smoking, and 2 alcoholic drinks per month.

*Elective Termination:* All 5 elective termination cases were reported to have occurred within 12 weeks of pregnancy. Cases were considered to be “elective” and no information on the presence or absence of fetal abnormalities was provided.

## 7.2.2 Discussion and Safety Findings

Based on safety analyses in 2266 ustekinumab-treated subjects with moderate to severe plaque psoriasis, ustekinumab appears to be safe and well tolerated.

- Common AEs generally occurred at similar rates in ustekinumab- and placebo-treated subjects, and were generally mild and self-limited. Rates of AEs did not increase with duration of exposure. There was no difference in the rate of AEs with self-administration versus health care administration.
- No adverse impact on psoriasis (eg, evidence of rebound psoriasis) or PsA was observed.
- No evidence of lymphocyte depletion or cumulative dosing toxicities was observed.
- Serious adverse events occurred at generally similar rates between ustekinumab- and placebo-treated subjects.

- Rates of serious infections and malignancies were low and similar between ustekinumab- and placebo-treated subjects, and the observed rates were consistent with the expected background rates.
- A numeric imbalance in rates of major adverse cardiovascular events was observed between ustekinumab- and placebo-treated subjects in the controlled portions of Phase 2 and 3 studies, resulting predominantly from an imbalance in event rates from a smaller Phase 2 study with 4:1 randomization. Analyses of event rates including all data through the BLA cutoff period failed to show a difference in subjects treated with ustekinumab, and rates of major adverse cardiovascular events were consistent with expected background rates.

### 7.3 Effect of Age

To evaluate the potential impact of age on the safety of ustekinumab, rates of AEs, SAEs, and AEs leading to study agent discontinuation were analyzed in age subpopulations using safety data pooled across the Phase 2 and 3 psoriasis studies. Through Week 12, rates of AEs, SAEs, and AEs leading to study agent discontinuation were generally comparable among groups within each age subpopulation analyzed. Through the data cutoff for the BLA, rates of AEs, SAEs, and AEs leading to study agent discontinuation were generally comparable between the 45 mg and 90 mg groups.

In subjects who were  $\geq 65$  years old, the proportion of subjects who had at least 1 AE during the placebo-controlled period was 45.8%, 73.2%, and 51.1% in the placebo, 45 mg, and 90 mg groups, respectively. Through the data cutoff for the BLA, similar rates of AEs, SAEs, and AEs leading to study agent discontinuation were observed between the 45 mg and 90 mg groups. Moreover, AE rates were generally comparable between age groups. Combined, these analyses do not suggest that age impacts the safety of ustekinumab, although limited safety knowledge exists in subjects  $\geq 65$  years old, and further information is required to definitively assess safety in this subpopulation.

### 7.4 Safety in Patients Outside Label Claim

In addition to studies in subjects with psoriasis, ustekinumab has also been studied in normal healthy volunteers and in subjects with PsA (70 placebo-treated subjects and 76 ustekinumab-treated subjects), MS (53 placebo-treated subjects and 216 ustekinumab-treated subjects), and Crohn's disease (52 placebo-treated subjects and 120 ustekinumab-treated subjects). Dosing in these studies was different than that studied in the psoriasis clinical study. Exposures studied in PsA and Crohn's disease were within the ranges of exposures studied in psoriasis. However, the range of doses studied in MS included much higher exposures than studied in psoriasis (up to 180 mg weekly x 4 doses followed by 180 mg q4w for a total of 19 weeks of dosing).

An evaluation of targeted AEs in other indications was generally consistent with the psoriasis population although the sample sizes in other indications were relatively smaller



than the Phase 2 and Phase 3 psoriasis population. No clinically significant safety signals were observed in the clinical studies in normal healthy volunteers or in subjects with PsA or Crohn's disease. Greater disparities in the rates of headache, fatigue, and injection site reactions between ustekinumab- and placebo-treated subjects were observed in the Phase 2 clinical study in MS than were observed in psoriasis clinical studies. However, SAE rates were comparable between ustekinumab- and placebo-treated subjects, and no adverse impact on the underlying disease (ie, MS) was observed.

There were no serious infections in the PsA study or either of the MS studies. In the Crohn's disease study, 2 serious infections were reported in ustekinumab-treated subjects: disseminated histoplasmosis in a subject febrile at baseline who had recently discontinued infliximab and infectious gastroenteritis.

No malignancies were reported in the PsA study. Three noncutaneous malignancies were reported in ustekinumab-treated subjects in the MS studies, one each breast, tonsil, and colon cancer, and one in the Crohn's disease study, prostate cancer.

No adjudicated major adverse or ischemic cardiovascular events were reported in the MS or Crohn's disease studies, though 1 subject in the MS study reported a stroke after the end of the follow-up period. In the PsA study, 1 MI was reported in a placebo-treated subject during the placebo-controlled period of the study (see Section 7.2.1.12.3).

## **7.5 Updated Data After BLA Submission (120-day Safety Update)**

Safety observations through 120-day safety period:

- A total of 2266 subjects were exposed to ustekinumab in the Phase 2 and 3 psoriasis studies. With incremental safety data available since the initial BLA, 1970 were exposed for at least 6 months, 1285 exposed for at least 1 year, and 373 exposed for at least 18 months. This data provides an additional 784 subject-years of follow-up (approximately 50% more) on ustekinumab (see Table 36).
- The profile of AEs observed with an additional 6 months of subject follow-up was consistent with the patterns and rates of AEs reported in the initial BLA.
- Duration of exposure or cumulative exposure to ustekinumab did not have an apparent impact on safety. Rates of AEs, SAEs, infections, and AEs leading to study agent discontinuation did not increase over time or with increasing length of exposure, and rates of these events did not appear to increase with increasing cumulative drug exposure.

- Rates of serious infections, malignancies, and serious cardiovascular events remained low with additional follow-up, and follow-up-adjusted rates of these events remained generally comparable to rates reported in the initial BLA (see Table 36).

**Table 36 Summary of event rates for serious infections, major adverse cardiovascular events, and incidence of neoplasm in Phase 2 and Phase 3**

	<u>Initial BLA</u> Ustekinumab			<u>120-day Safety Update</u> Ustekinumab		
	45 mg	90 mg	Combined	45 mg	90 mg	Combined
Subjects treated <sup>a</sup>	1110	1156	2266	1110	1156	2266
Total subject years of follow-up <sup>b</sup>	725	742	1467	1113	1138	2251
Event rate per hundred subject-years (number of events)						
Serious infections	0.83 (6)	1.21 (9)	1.02 (15)	1.08 (12)	1.05 (12)	1.07 (24)
Major adverse cardiovascular events <sup>c</sup>	0.69 (5)	0.54 (4)	0.61 (9)	0.54 (6)	0.35 (4)	0.44 (10)
Incidence rate per hundred subject-years (number of subjects)						
Neoplasms (malignant)	1.52 (11)	1.08 (8)	1.30 (19)	1.26 (14)	1.06 (12)	1.16 (26)
NMSC	0.83 (6)	1.08 (8)	0.96 (14)	0.63 (7)	0.97 (11)	0.80 (18)
Malignancy other than NMSC	0.69 (5)	0.00 (0)	0.34 (5)	0.63 (7)	0.09 (1)	0.36 (8)
Lymphoma	0	0	0	0	0	0

<sup>a</sup> Placebo crossover subjects were included in ustekinumab columns after crossover to ustekinumab.

<sup>b</sup> The total subject years of follow-up for malignancy is slightly lower since only the first event is counted in the calculation of incidence per 100 subject-years.

<sup>c</sup> Major adverse cardiovascular events include cardiovascular death, MI, or stroke.

Additionally, preliminary safety data are also available comparing 12 weeks of treatment with ustekinumab versus etanercept in 903 subjects with moderate to severe plaques psoriasis (ustekinumab 45 mg [n = 209] or 90 mg [n = 347] at Weeks 0 and 4 versus etanercept 50 mg twice per week [n = 347] for 12 weeks). Ustekinumab and etanercept were both well tolerated through Week 12.

Specific safety findings included the following:

- The proportions of subjects with AEs were comparable across treatment groups (66.0% and 68.3% for the ustekinumab 45 mg and 90 mg groups, respectively, versus 69.5% in the etanercept group). The pattern of AEs was generally comparable between groups, though rates of injection sites reactions (all nonserious) were higher in the etanercept group (22.2%) than the ustekinumab groups (2.9% and 2.0% in the 45 mg and 90 mg groups, respectively).
- No deaths occurred in the study.
- Four subjects in each treatment group reported at least 1 SAE:
  - Ustekinumab 45 mg group: 1 subject with alcoholic pancreatitis; 1 subject with chest pain and hypertension; 1 subject with breast cancer; and 1 subject with a psychotic disorder.
  - Ustekinumab 90 mg group: 1 subject with appendicitis; 1 subject with uvulitis; 1 subject with gastrointestinal infection; and 1 subject with urosepsis with complicating acute renal failure, myocardial infarction (adjudicated as no event), nosocomial pneumonia, and upper GI bleed;
  - Etanercept group: 1 subject with bacterial meningitis; 1 subject with upper abdominal pain; 1 subject with nephrolithiasis; and 1 subject with rotator cuff syndrome.
- Three subjects reported NMSCs, 2 subjects in the 45 mg ustekinumab group and 1 subject in the 90 mg ustekinumab group, all of which occurred in sites of psoriasis that cleared with treatment.
- The proportions of subjects with AEs leading to study agent discontinuation were 1.9% and 1.2% for the ustekinumab 45 mg and 90 mg groups, respectively, versus 2.3% in the etanercept group.
- No cases of TB or serious opportunistic infections were observed.

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## 8 Overall Benefit/Risk Profile

### 8.1 Unmet Medical Needs

The current treatment recommendations suggest that topical therapy should be employed for localized psoriasis and that phototherapy or systemic agents be considered for moderate to severe plaque psoriasis. Currently approved small molecule systemic agents (MTX, cyclosporine, and acitretin) have safety limitations, including organ toxicity, infection, malignancy, and teratogenicity that limit their usefulness in the long-term management of psoriasis, though some (eg, cyclosporine) are highly effective. PUVA is associated with an increased risk of skin malignancies, including melanoma, imposes significant lifestyle restrictions on patients with frequent visits to specialized phototherapy units and avoidance of sun exposure, and is not suitable for continuous long-term chronic psoriasis management because of cumulative photo-damage. Five biologic agents have been approved for the treatment of psoriasis. These agents, in general, have not been associated with organ toxicity or teratogenicity, though each may be accompanied by drug-specific safety concerns (eg, infection, malignancy, and demyelinating neurologic events).

Additionally, some systemic agents, both conventional and biological, have limited efficacy, with fewer than half of subjects achieving higher levels of response despite risk associated with them. Further, long-term efficacy data in many systemic agents is limited. Finally, most systemic agents must be administered at least weekly. Therefore, for patients with moderate to severe plaque psoriasis who require treatment with a systemic agent, an unmet need remains for highly effective, safe, and convenient therapies.

### 8.2 Benefits and Risks of Ustekinumab

Three adequate, well-controlled studies consistently demonstrated that ustekinumab was highly effective in treating subjects with moderate to severe plaque psoriasis with efficacy levels consistent with the most efficacious conventional systemic and biologic agents. Ustekinumab was highly effective across all demographic subpopulations, across the spectrum of moderate to severe disease, and regardless of prior use of or experience with phototherapy or other systemic agents. Ustekinumab was highly effective in ameliorating psoriatic plaques, pruritus, and nail psoriasis, and additionally improved dermatology-specific and general quality of life measures, as well as anxiety, depression, and work limitations and productivity. Many subjects indicated that psoriasis had no detectable impairment on their quality of life during active treatment.

Clinical response was maintained in most subjects through at least 1 year. The therapeutic benefits were achieved with q12w dosing, a dosing schedule that offers a new level of convenience for patients and physicians and regardless whether ustekinumab was administered by a health care professional or self-administered. These attributes may be particularly important for treatment compliance, which is low in patients with psoriasis,

at least in part due to dissatisfaction with effectiveness and/or convenience of currently available treatments ([Stern et al, 2004](#); [Richards et al, 2006](#)).

Treatment with ustekinumab was well-tolerated. Adverse events were generally mild, nonserious events that did not require treatment discontinuation. No organ toxicity was observed, and no adverse impact on routine laboratory parameters was observed. No cases of salmonella or non-tuberculous mycobacterial diseases were reported, and no cases of active TB were reported. Rates of serious infections and malignancies, a theoretical risk of all immunosuppressive drugs, were low and similar between ustekinumab- and placebo-treated subjects, and the observed rates were consistent with the expected background rates. The pattern of malignancies observed, including the ratio of basal cell:squamous cell skin cancers did not suggest a pattern of immunosuppression. A numeric imbalance in major cardiovascular events during the placebo-controlled period resulted predominantly from events observed in the Phase 2 study in which the subject allocation was also imbalanced. Additional analyses failed to provide confirmatory evidence suggesting an impact of ustekinumab on cardiovascular risk, and nonclinical analyses did not suggest a mechanistic basis for an impact of ustekinumab on cardiovascular risk. Though considered improbable, it is not possible to exclude a potential impact of ustekinumab on cardiovascular risk.

Overall, the benefit-risk profile of ustekinumab is favorable for patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. While the large safety experience resulting from the clinical study program of ustekinumab provides a good understanding of potential risks, a larger population experience will be required to evaluate the potential impact of ustekinumab on rare AEs and to further define any impact on uncommon SAEs, including malignancies, serious infections, and cardiovascular events. Centocor is committed to further define the safety of ustekinumab with observational studies and to appropriately educate and inform patients about potential risks of ustekinumab.

### **8.3 Basis for Dosing Recommendations**

The dosing recommendations for ustekinumab are intended to optimize therapeutic efficacy while minimizing unnecessary drug exposure. The 90 mg dosing regimen of ustekinumab showed greater efficacy than the 45 mg dosing regimen. However, the disparity in efficacy resulted primarily from efficacy differences in subjects weighing more than 100 kg, in whom the 90 mg regimen provided efficacy levels approximately 15 to 20 percentage points higher than the 45 mg regimen. This magnitude of efficacy difference, combined with a lack of any apparent impact of dose on safety, is considered clinically meaningful to warrant a recommendation for treatment with the 90 mg dose in subjects > 100 kg in weight.

Psoriasis is a chronic disease, and while ustekinumab was highly effective in controlling psoriasis, the randomized withdrawal analysis demonstrated that discontinuation of treatment resulted in return of disease. Within 12 weeks of a missed dose, response rates

began to diminish by a variety of PASI and PGA response measures in subjects withdrawn from drug, and maintenance of PASI 75 response was significantly lower compared to subjects in whom ustekinumab was continued. These observations demonstrate that maintaining control of psoriasis will require maintenance therapy in most patients, and the level of treatment effect observed, combined with a lack of any apparent impact of long term maintenance dosing on safety for at least 1 year, is clinically meaningful to warrant continuous maintenance dosing.

Based on these considerations, the following dosing is recommended:

- Ustekinumab is administered by subcutaneous injection.
  - For patients weighing  $\leq 100$  kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by dosing every 12 weeks.
  - For patients weighing  $> 100$  kg, the recommended dose is 90 mg initially and 4 weeks later, followed by dosing every 12 weeks.

In patients weighing  $> 100$  kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these patients.

These dosing recommendations will optimize initial efficacy and maintain psoriasis control in the majority of subjects while limiting drug exposure. Heavier patients (ie, patients  $> 100$  kg) receive a higher dose (90 mg) that leads to serum drug levels comparable those achieved in lighter patients (ie, patients  $\leq 100$  kg) who receive the 45 mg dose.

## **8.4 Risk Management Plan**

A Risk Management Plan has been developed in order to maximize the benefit and minimize the risk of ustekinumab use in the postmarketing setting. As noted in Section 7.2.1.10, potential safety risks have been identified and warrant additional follow-up, as well as risk minimization activities. These potential risks are serious infections, malignancy, cardiovascular events, and serious systemic hypersensitivity reactions. In addition, it is recognized that exposure during pregnancy may also be a potential risk in the postmarketing setting.

### **8.4.1 Pharmacovigilance**

The potential risks listed above will be monitored in the postmarketing setting in a variety of ways. Through these activities, additional safety data will be collected and assessed.

#### **8.4.1.1 Pharmacovigilance Activities**

The objective of the Company's pharmacovigilance strategy is to systematically collect AEs from multiple sources and to conduct real time and periodic medical assessments of single and aggregate cases to identify potential safety signals. The detection and evaluation of changes in reporting frequency of AEs and changes in overall AE pattern suggestive of potentially new safety concerns enables the Company to develop and implement appropriate risk management strategies.

Comprehensive pharmacovigilance activities are utilized to monitor spontaneous AE reporting of ustekinumab in the postmarketing setting. These include:

- Adverse event collection and single case processing
  - Collection of spontaneous AE reports and clinical SAEs in a centralized and validated company safety database (SCEPTRE).
  - Performance of real-time medical review to identify important single cases and conduct of appropriate follow-up to obtain relevant medical information.
  - Preparation and submission to health authorities, including the FDA, of all Expedited Reports and other reports of interest within specified time frame.
  - Distribution of AEs to operating companies for health authority reporting, according to local regulations.
- Aggregate Reports
  - Health Authority Specified Reports: Aggregate reports are prepared and submitted to health authorities as required by regulations. These include Periodic Safety Update Reports (PSURs), New Drug Application Periodic Adverse Drug Experience Reports (NDA PADER), Annual Safety Reports and other reports as required.
  - Ad-hoc or Interim Reports on Specified Topics as Requested or Agreed: Ad hoc reports are prepared upon identification of a potential safety issue and/or upon request by a regulatory agency or other healthcare customer.
  - Other Summary Reports: This includes relevant safety information from clinical, epidemiology and external data sources.

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- Safety surveillance and signal detection
    - The Safety Surveillance Group is a specialized group within J&J that has responsibility for conducting periodic medical review of aggregate postmarketing data from internal and external safety databases to detect new signals. Key surveillance activities include:
      - Intra-product signaling: Periodic review of AE frequency reports from SCEPTRE to identify shift changes in AE reporting frequency, reporting proportion (relative reporting of a selected AE as a proportion of all AE reports for the drug for a defined time period) and reporting pattern over time.
      - Inter-product signaling: Periodic review of regulatory databases, using data mining tools to identify disproportionalities (observed frequency for selected drug is greater than expected frequency based on all other drugs in the database). Examples of these databases are the US Food & Drug Administration's public release safety database (FDA Adverse Event Reporting System/Spontaneous Reporting System [AERS/SRS]) and the WHO Drug Monitoring Center's safety database (WHO Vigibase).
  - A follow-up questionnaire utilized to obtain more complete information for targeted spontaneous reports.

#### **8.4.1.2 Clinical Study Data**

Clinical study data is an important means of obtaining safety information. Several clinical studies are underway or are planned as follows:

- Long-term extensions of the two Phase 3 psoriasis studies are ongoing and will provide important safety data around the effects of ustekinumab over a period of up to 5 years.
  - A total of 1996 subjects were randomized into these 2 studies.
  - Assuming a 10% attrition rate each year from the original group (1996 subjects), approximately 200 subjects per year will be lost.
  - With a 10% attrition rate, the long-term extensions are estimated to result in a total follow-up of approximately 7500 subject-years.



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- These long-term extensions, combined with the currently available safety experience, will provide better estimates of rates of uncommon AEs in ustekinumab-treated subjects with moderate to severe plaque psoriasis, and will also provide insight into the potential impact of ustekinumab on rare AEs.
  - An etanercept comparator study is underway and will be able to provide AE rates compared with an anti-TNF therapy currently in use for psoriasis.
  - A Phase 2b study in Crohn's disease is planned and will enable analysis of the safety profile in another patient population.

### **8.4.1.3 Observational Studies**

In addition to the ongoing and planned clinical studies, Centocor will be assessing safety data in 3 large postmarketing safety studies using a prospective disease-specific registry and external databases. These programs, in conjunction with the long-term extensions of the Phase 3 studies, create a program that incorporates both active surveillance and in-depth targeted follow-up of AEs not necessarily limited to indication.

#### **8.4.1.3.1 PSOLAR (PSOriasis Longitudinal Assessment and Registry)**

PSOLAR is an international, multicenter, open registry of patients with psoriasis based in North America, currently expanding to approximately 500 sites internationally. The key features are:

- Comparator cohort:
  - Approximately 4000 patients exposed to ustekinumab
  - Patients on biologic therapies
    - Infliximab
    - Other systemic biologics
  - Patients on systemic therapies [other than biologics]
  - Patients on photo/topical therapies
- Demographics:
  - Anticipating approximately 60% of patients from North America (Canada/ United States).
  - Approximately 20% of patients from the European Union (North, Central, Southern) and western Asia.
  - Approximately 20% of patients from eastern Asia.

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- Actively collect all serious AEs and other targeted AEs including:
    - Specific infections: TB, opportunistic infections, PML, salmonella
    - Malignancies
    - Cardiovascular events
    - Exposure during pregnancy
    - Adverse reactions to vaccines
    - Neurologic or demyelinating events
  - Collect data on disease activity, patient-reported outcomes, and specific health economics measures.
  - Treatment will be prescribed by the physician according to actual clinical practice or standard of care for psoriasis.
    - No randomized assignments to treatment and no restrictions on the use of concomitant medications.
    - By collecting data on psoriasis patients that are eligible to receive systemic therapies, it provides the ability to investigate therapies in actual clinical use.
    - Ability to capture patient characteristics and outcomes even if they have an intolerance of, or elect to avoid, the therapy preferred by their physician.
  - Eight-year course of observation from enrollment of last subject.
    - Interim analyses will be conducted at least annually throughout the registry period, beginning 1 year after the start of enrollment.
    - Data from the analyses will be summarized in annual reports. These reports will also be reviewed by a steering committee that will meet twice yearly.
  - The ability to collect data combining longitudinal observations of safety and additional clinical observations beyond those routinely used for clinical care will better characterize subjects receiving treatment for psoriasis in academic and community-based clinical practices.
  - Actively managed by a large chartered steering committee with international external (non-industry) clinician researchers and epidemiologists.
    - Ability to react to the needs or concerns of the dermatology community is a key aspect of its design.
    - Steering committee is charged with optimizing registry conduct to maximize the appropriate collection of safety and outcomes information.

In summary, a main objective of the registry is to evaluate the safety of ustekinumab in patients utilizing a disease-based approach that collects comparable information from patients with psoriasis who are eligible to receive systemic therapies other than ustekinumab. A secondary objective is to collect in-depth information on any perceived covariables that may be related to disease activity. While one must acknowledge that registries may not have the ability to evaluate rare events or identify lower relative risks, they nonetheless provide a key mechanism to explore and identify new safety concerns. For example, with 4000 ustekinumab treated patients and 4000 comparator group patients tracked for an average of 4 years of use, an increase in the AE rate from the comparator rate of 1% to 1.5% could be discriminated with a power of 98%.

#### **8.4.1.3.2 Nordic Database Initiative**

Registries like PSOLAR provide an important component to sentinel safety programs, but they are subject to patient participation. To better insure the capture of safety data in a large population, studies that actively capture outcomes using a larger observational cohort are a very helpful. While they may not always contain as much information on covariates as a targeted registry program, they can offer an improved ability to capture more rare events. Furthermore, they represent total patient capture of clinical care which avoids many of the biases of prospective enrollment. In this context, an evaluation of the Northern European Swedish national (whole population) medical and pharmaceutical data sets has been proposed. This dataset, in conjunction with allied datasets from Northern Europe, have been used successfully in previous studies of the outcomes of patients exposed to biologics.

- Prospective, 5-year observational study of AEs observed in patients in actual clinical practice, independent from prescriber or patient participation.
- Utilizes multiple Northern European registries in unison since they may be cross-referenced by individual patients.
- Opportunity for surveillance on a population that exceeds 9 million people
  - Sample size will depend on actual clinical use.
  - Projecting 3% of adults within the registers with psoriasis and assuming approximately 5% eligible for ustekinumab, the exposure cohort may be approximately 11,000 patients.
  - In combination with PSOLAR would likely provide an overall sentinel network with > 30,000 patient years of ustekinumab versus > 30,000 patient years of other therapies that could potentially detect an increased risk for an AE with a baseline rate of 1% and a relative risk of 1.3 at a power of 93%.

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- A commensurate control group of patients exposed to other biologics or oral systemic agents is available for analysis amongst Swedish national health registries which have previously been accessed by Centocor for analysis of pregnancy outcomes (see Section 8.4.1.4).
    - Swedish Medical Birth Register
    - Swedish Prescription Drug Register
    - Swedish Hospital Discharge Register.
  - Active surveillance strategy captures data on AEs reported with ustekinumab across indications.
  - Comparator cohorts including other systemic therapies (including biologics)
    - Disease and healthy controls are available within the same dataset.
  - The analysis will have two key aspects:
    - Collection and analysis of information pertaining to AEs of patients exposed to ustekinumab, relative to the background risk in similar but non-biologic exposed patients.
    - Collection and analysis of information pertaining to AEs of patients exposed to systemic agents that include biologics used to treat psoriasis (other than ustekinumab), relative to the background risk in similar but non-biologic exposed patients.
  - An analysis will be performed with any exposure, then a sensitivity analysis with increasing level of exposure.
  - Annual reports will delineate:
    - Descriptive statistics of AEs of interest in the target cohorts.
    - Comparison of AEs by disease/indication of interest, with and without ustekinumab exposure.
    - If sentinel AE outcomes are noted from this program, there is an opportunity to coordinate additional evaluations through the PSOLAR registry's steering committee. As such, the programs have the ability to act in unison in a coordinated fashion to explore signals of interest.

In summary, this surveillance strategy offers the opportunity to perform surveillance on a large population likely to have access to not only ustekinumab but also a variety of other prior or concurrent therapies. This type of population is necessary to insure the ability to investigate effects of combinations of therapies, even when administered off-label.

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#### 8.4.1.4 Pregnancy Research Initiative

To better insure collection of the outcomes of pregnancy in those exposed to ustekinumab, a specific program will be undertaken that actively captures these events in a large population. Since pregnancy during treatment with biologic therapy is presumably a rare event, it requires special attention to obtain sufficient numbers of observation to explore both maternal and fetal outcomes.

- It is a prospective, 5-year observational study of pregnancy outcomes using 3 national registry systems in Sweden, Finland and Denmark. This study accesses the following resources:
  - Swedish national health registries: Swedish Medical Birth Register, Swedish Prescription Drug Register, and Swedish Hospital Discharge Register.
  - Danish national health registries: Danish Medical Birth Register, Danish Register of Medicinal Product Statistics, Danish National Patient Registry.
  - Finnish national health registries: Finnish Medical Birth Register, Finnish Register on Prescribed Medicine, Finnish Hospital Discharge Register, Finnish Register on Induced Abortions, Finnish Register on Congenital Malformations.
- Pregnant women with prenatal exposure to ustekinumab in actual clinical practice will be assessed versus a comparable disease-matched control group of pregnant women without exposure to ustekinumab.
- The health status of their infants who have had prenatal exposure to ustekinumab during a one-year follow-up period will be assessed versus unexposed controls.
- Treatments are captured as prescribed by the physician per usual clinical practice from 3 months prior to conception through birth.
- Perinatal information is available from the first prenatal care visit through post-delivery hospital discharge. Information will be gathered prospectively during this period and will be available for analysis once it has been entered into the Swedish, Danish, or Finnish Medical Birth Registers after birth.
- Annual reports will summarize:
  - Collection and analysis of information pertaining to pregnancy outcomes of women exposed to ustekinumab during pregnancy, relative to the background risk in similar but non-biologic exposed patients

- Collection and analysis of information about the health status of infants during the first year following delivery. Specifically, this includes information about infants with prenatal exposure to ustekinumab and infants born to women with diseases of interest but without prenatal exposure to infliximab.
- A similar protocol has been an effective active surveillance strategy for pregnancy in the context of inadvertent exposure to infliximab when becoming pregnant.

In summary, this active surveillance program utilizes a large population database that will provide access to patients exposed to ustekinumab during pregnancy, as well as information about infants exposed in utero for up to one year after birth.

#### **8.4.2 Risk Minimization Activities**

The Company is committed to implementing measures that will inform and educate both physicians and patients. Risk minimization activities include:

- The proposed ustekinumab United States Package Insert (USPI) includes safety information.
- A comprehensive education plan for both physicians and patients is being developed:
  - Education regarding the risk of serious infections and malignancy;
  - Education regarding the risk of cardiovascular disease and cardiovascular risk factors in the psoriasis population.

The use of these measures will allow for safe and effective use of ustekinumab in the postmarketing setting.

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## **10 Appendices**

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## Appendix A Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index or PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of the disease is calculated as follows.

In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20%, and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and scaling, which are each rated on a scale of 0 to 4.

The scoring system for the signs of the disease (erythema, induration, and scaling) are: 0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

0 = no involvement

1 = 1% to 9% involvement

2 = 10% to 29% involvement

3 = 30% to 49% involvement

4 = 50% to 69% involvement

5 = 70% to 89% involvement

6 = 90% to 100% involvement

To help with the area assessments, the following conventions should be noted:

The neck is considered part of the head

The axillae and groin are part of the trunk

The buttocks are part of the lower extremities

The PASI formula is:

$$\text{PASI} = 0.1 (E_h + I_h + S_h) A_h + 0.3 (E_t + I_t + S_t) A_t + 0.2 (E_u + I_u + S_u) A_u + 0.4 (E_l + I_l + S_l) A_l$$

Where E = erythema, I = induration, S = scaling, and A = area



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## Appendix B Relative Physician's Global Assessment

The relative PGA documents the physician's assessment of the subject's psoriasis status. Consideration should be given to the percent of body involvement as well as overall induration, scaling, and erythema. The PGA is assessed relative to baseline condition and is defined as: (1) = clear, (2) = excellent, (3) = good, (4) = fair, (5) = poor, and (6) = worse. The following table further defines the rating.

Rating	% Clearing	Definition of Response
1 = Clear	100% clear	Some residual pinkness or pigmentation: Wornoff's ring may be present.
2 = Excellent	75 to 99% clearing	Marked improvement: nearly normal skin texture; some erythema may be present.
3 = Good	50 to 74% clearing	Moderate improvement: plaque has cleared to point of small scattered papules with normal intervening epidermis.
4 = Fair	25 to 49% clearing	Slight improvement: decrease in scaling and softening of plaque.
5 = Poor	0 to 24% clearing	Little or no change in scaling, erythema, or plaque elevation.
6 = Worse		Worse

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## Appendix C Static Physician's Global Assessment

The static PGA is used to determine the subject's psoriasis lesions overall at a given time point. Overall lesions will be graded for induration, erythema, and scaling based on the scales below. The sum of the 3 scales will be divided by 3 to obtain a final PGA score.

**Induration (I)** (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement)

- 0 = no evidence of plaque elevation
- 1 = minimal plaque elevation, = 0.25 mm
- 2 = mild plaque elevation, = 0.5 mm
- 3 = moderate plaque elevation, = 0.75 mm
- 4 = marked plaque elevation, = 1 mm
- 5 = severe plaque elevation, = 1.25 mm or more

**Erythema (E)** (averaged over all lesions)

- 0 = no evidence of erythema, hyperpigmentation may be present
- 1 = faint erythema
- 2 = light red coloration
- 3 = moderate red coloration
- 4 = bright red coloration
- 5 = dusky to deep red coloration

**Scaling (S)** (averaged over all lesions)

- 0 = no evidence of scaling
- 1 = minimal; occasional fine scale over less than 5% of the lesion
- 2 = mild; fine scale dominates
- 3 = moderate; coarse scale predominates
- 4 = marked; thick, nontenacious scale dominates
- 5 = severe; very thick tenacious scale predominates

**Add  $I + E + S =$  \_\_\_\_\_ / 3 = \_\_\_\_\_ (Total Average)**

**Physician's Static Global Assessment based upon above Total Average**

- 0 = Cleared, except for residual discoloration
- 1 = Minimal - majority of lesions have individual scores for  $I + E + S / 3$  that averages 1
- 2 = Mild - majority of lesions have individual scores for  $I + E + S / 3$  that averages 2
- 3 = Moderate - majority of lesions have individual scores for  $I + E + S / 3$  that averages 3
- 4 = Marked - majority of lesions have individual scores for  $I + E + S / 3$  that averages 4
- 5 = Severe - majority of lesions have individual scores for  $I + E + S / 3$  that averages 5

Note: Scores should be rounded to the nearest whole number. If total  $\leq 1.49$ , score = 1; if total  $\geq 1.50$ , score = 2.

## Appendix D External Databases

The following external databases were selected to estimate expected event rates of targeted events:

- For comparisons with the general population:
  - The National Institutes of Health Surveillance, Epidemiology, and End Results (**SEER**) database (2004) – a well-established cross-sectional study used to evaluate expected rates of noncutaneous malignancies (adjusting for age, sex, and race).
  - **Framingham Heart Study** – a widely recognized and established cohort study used to evaluate expected rates of cardiovascular events (adjusting for underlying cardiovascular risk factors such as age, gender, diabetes, smoking history, total cholesterol, HDL cholesterol, blood pressure).
  - **Center for Disease Control (CDC)** – the CDC database (CDC: Health, United States, 2006 with Chartbook on Trends in the Health of Americans) used to evaluate expected rates of cardiovascular events in a general US population after adjusting for age and gender
- For comparisons with the psoriasis population:
  - **MarketScan claims database** – A claims database including more than 10 million covered lives up to 2004, from which a cohort of 1183 psoriasis patients was used to estimate the expected rate of hospitalizations and infections requiring hospitalizations in patients with psoriasis who were treated with systemic agents.
  - **General Practice Research Database (GPRD) database** – A medical records database in the UK established for epidemiologic research that was used to evaluate expected rates of cardiovascular events specifically in patients with psoriasis who were treated with systemic agents (also adjusting for underlying cardiovascular risk factors).
  - **Data from clinical trials of other biologics** - These cross-study analyses using publicly available data allow for a comparison of the rates of targeted AEs in clinical studies of ustekinumab to those observed in subjects with similar demographics and disease characteristics participating in clinical trials of other approved biological agents.