

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**125261**

**MEDICAL REVIEW(S)**

COMPLETED SEP 02 2009

Review and Evaluation of Clinical Data COMPLETED SEP 02 2009

---

BLA (Serial Number)	125261
Sponsor:	Centocor Ortho Biotech Inc.
Drug:	Stelara Liquid in vial (ustekinumab)
Proposed Indication:	Psoriasis
Material Submitted:	Consultation request
Correspondence Date:	8/11/09
Date Assigned:	8/12/09
Date Review Completed:	8/17/09
Reviewer:	Jody Green, MD. Medical Reviewer, DNP, ODE I

---

## 1. Introduction

An approval action is pending for a monoclonal antibody product that blocks IL12 and IL23 and that treats plaque psoriasis in adults, Stelara (ustekinumab). In review of the application, it was noted by the Division of Dermatology and Dental Products that there was a case of posterior reversible encephalopathy syndrome (PRES) reported in a 65-year-old female in a pivotal trial. They are requesting advice from the Division of Neurologic Products on where and how to describe this event in labeling.

The material submitted and reviewed includes the following:

- case report
- proposed label
- sponsor-provided response to FDA Request for Information
- bibliography

## 2. Material submitted

### 2.1 Case report provided by sponsor

Subject C0743T09 006-017 is a 63-year-old woman with a 26-year history of psoriasis as well as a history of alcohol abuse. She was enrolled in the ustekinumab trial on April 26, 2006 at a dose of 45 mg subcutaneously as per protocol. She was treated approximately every 12 weeks for a total of 12 doses. Her last dose was September 11, 2008. On \_\_\_\_\_ years after starting treatment with ustekinumab, she presented to an Emergency Room (ER) with nausea, vomiting, headache, and seizure along with confusion. She had two witnessed seizures in the ER. Her blood pressure was noted to be elevated at 152/92. A CT scan with and without contrast showed a left thalamic hypodensity as well as some white matter changes in the cerebellar region without any evidence of an acute stroke or hemorrhage. An MRI scan showed similar abnormalities with hyperintensities in the cerebral hemisphere and the upper portion of the left thalamus as well as in the right and possibly the left parietal periventricular white matter. A CT angiogram showed no evidence of vasospasm or other abnormality. An EEG showed some slowing of 6-7 Hertz but no epileptiform activity. A spinal tap was normal with the exception of a mildly increased protein of 87 mg/dL. PCR for HSV, West Nile and JC virus were negative. Treatment included supportive care including anti-convulsant therapy. At discharge from the hospital \_\_\_\_\_ later, she was clinically improved. By final visit, she had returned to baseline status without residual deficit including a normal MRI.

b(6)

b(6)

### 2.2 Sponsor's Opinion

According to \_\_\_\_\_, Neurologist and External Consultant, the most likely diagnosis for this patient was PRES. Although at the time of hospital admission the leading diagnosis was alcohol withdrawal seizures, this was later considered unlikely as the patient showed no other symptoms suggestive of a withdrawal syndrome. In addition, the MRI had significant acute findings, which rapidly resolved with supportive care, which is characteristic of PRES but not stroke or PML. Since the patient had received ustekinumab, and had a history of an autoimmune disease (psoriasis), as well as alcohol abuse, it was unclear what role the drug played in triggering her condition.

b(4)

### 2.3 Literature review

PRES was first described by Hinchley in 1996 and since then has also been described in multiple case reports and in a case series. This syndrome is recognized because of its MRI findings, which are typically striking. The characteristic location of MRI findings is hyperintensities most commonly in the white matter, but also in the grey matter in the T2-weighted sequences in the parieto-occipital lobes. There has been some variability of radiographic findings that have been reported, but the findings are generally most prominent posteriorly. Particularly characteristic of the syndrome is the complete resolution of radiologic findings over time, often quite rapidly.

The findings seen on neuroimaging in PRES are felt to represent vasogenic edema as a result of endothelial dysfunction and vasculopathy. Arising from leaky capillaries, the edema can be caused by drugs that affect the endothelium either directly or secondarily as a consequence of increasing blood pressure or blood volume. As noted by the sponsor, nothing is presently known about ustekinumab to suggest that it would cause this type of change in cerebral perfusion and endothelial function. Other drugs which have been associated with PRES, such as bevacizumab and cyclosporine, have more plausible mechanisms as they have been associated with hypertension and vasoconstriction.

Various associations have been described in the literature for PRES. In a retrospective analysis, Lee reported that out of 38 episodes identified, co-morbid conditions or associations included hypertension (68%), renal disease (45%), dialysis dependency (21%), malignancy (32%), transplantation (24%), alcoholism (16%), and eclampsia (11%). Additionally there have been numerous case reports in the literature that cite coexisting preeclampsia, eclampsia, immunosuppressive drugs, immune-mediated diseases such as lupus, and even a case report of a patient with psoriasis treated with cyclosporine.

### 3. Reviewer's Comments

In the case reported by this sponsor, the presentation, time course of resolution, full recovery, all are consistent with the diagnosis of PRES. The MRI features are not inconsistent with the diagnosis: although a bit atypical in location, they are well within the range described in the literature. Much as other cases reported in the literature, more than one potential association confounds this case. This individual had an immune disorder (psoriasis) as well as a history of

alcoholism, both of which have been reported to be associated with this condition. Hence, it is premature at this point to say that ustekinumab caused PRES based on a single case in a large series, which is confounded by other factors.

#### **4. Recommendations**

We recommend that this case be described as a line-listing in the Clinical Trials section under Adverse Events rather than in the Warnings and Precautions section. This recommendation is made because no causal relationship can be made between PRES and ustekinumab administration at this time with only a single confounded case.

If the Division of Dermatology and Dental Products should wish to place a description of this event in the Warnings and Precaution section of the label, then we do have some suggestions about the wording for that section. Wording of the adverse event should mention that reversible posterior leukoencephalopathy syndrome (RPLS), otherwise known as posterior reversible encephalopathy syndrome (PRES), is a neurological disorder, which typically presents with visual disturbance, seizures, confusion, and headache. These symptoms as well as the characteristic changes seen on brain MRI are typically reversible. The condition may be associated with preeclampsia, eclampsia, acute hypertension, immunosuppressive therapy as well as other factors. Treatment involves supportive care, including treatment of hypertension and seizures if appropriate.

#### **5. References**

Cosottini, M, et.al. Cyclosporine-related PRES in non-transplant patient: a case report and literature review. *European Journal of Neurology*. 2003; 10 (4): 461-464.

Hinchley J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *New England Journal of Medicine*. 1996; 334(8): 494-500.

Hinchley J, Reversible Posterior Leukoencephalopathy Syndrome: what have we learned in the last 10 years? *Archives of Neurology*. 2008; 65(2):175-176.

Lee VH, et al, Clinical spectrum of reversible posterior leukoencephalopathy syndrome. *Archives of Neurology*. 2008; 65(2): 205-210.

Leroux G, et al, PRES during systemic lupus erythematosus: four new cases and review of the literature. *Lupus*. 2008;17(2):139-47.

Levy CF, et al, PRES syndrome in a child treated with bevacizumab. *Pediatric Blood Cancer*. 2009; 52(5): 669-71.

Servillo, Giuseppe, et al, PRES in intensive care medicine. *Intensive Care Medicine*. 2007; 33: 230-236.



---

Jody Green, MD.  
Medical Reviewer – DNP ODE I



---

Eric Bastings, MD  
Acting Team Leader- DNP ODE I  
Deputy Division Director

8/17/09

cc:

HFD-120

BLA 125261

## CLINICAL REVIEW

*Final*

Application Type BLA  
Submission Number 125261  
Submission Code 00

*Brenda Carr M.D. 22 July 09  
Full Final Show 7.22.09*

Letter Date January 9, 2009  
Stamp Date January 9, 2009  
PDUFA Goal Date October 9, 2009

Reviewer Name Brenda Carr, M.D.  
Review Completion Date July 16, 2009

Established Name ustekinumab  
(Proposed) Trade Name Stelara  
Therapeutic Class IL-12/IL-23 antagonist  
Applicant Centocor Ortho Biotech, Inc.

Priority Designation P

Formulation solution for subcutaneous administration  
Dosing Regimen Weeks 0, 4 then every 12 weeks  
Indication treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

Intended Population adult patients (18 years or older)

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT</b>	<b>4</b>
1.1	Recommendation on Regulatory Action	4
1.2	Risk Benefit Assessment	4
1.3	Recommendations for Postmarketing Requirements	5
1.4	Recommendations for other Post Marketing Study Commitments	7
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND</b>	<b>8</b>
2.1	Product Information	8
2.2	Tables of Currently Available Treatments for Proposed Indications	8
2.3	Availability of Proposed Active Ingredient in the United States	8
2.4	Important Safety Issues With Consideration to Related Drugs	8
2.5	Summary of Presubmission Regulatory Activity Related to Submission	8
2.6	Other Relevant Background Information	9
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES</b>	<b>9</b>
3.1	Submission Quality and Integrity	9
3.2	Compliance with Good Clinical Practices	15
3.3	Financial Disclosures	15
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES</b>	<b>15</b>
4.1	Chemistry Manufacturing and Controls	15
4.2	Clinical Microbiology	16
4.3	Preclinical Pharmacology/Toxicology	16
4.4	Clinical Pharmacology	16
4.4.1	Mechanism of Action	16
4.4.2	Pharmacodynamics	16
4.4.3	Pharmacokinetics	16
<b>5</b>	<b>SOURCES OF CLINICAL DATA</b>	<b>16</b>
5.1	Tables of Clinical Studies	16
5.2	Review Strategy	16
5.3	Discussion of Individual Studies	17
<b>6</b>	<b>REVIEW OF EFFICACY</b>	<b>18</b>
6.1	Indication	18
6.1.1	Methods	18
6.1.2	Demographics	18
6.1.3	Patient Disposition	19
6.1.4	Analysis of Primary Endpoint(s)	19
6.1.5	Analysis of Secondary Endpoints(s)	19
6.1.6	Other Endpoints	19
6.1.7	Subpopulations	19
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	19
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects	19
6.1.10	Additional Efficacy Issues/Analyses	19
<b>7</b>	<b>REVIEW OF SAFETY</b>	<b>20</b>
7.1	Methods	20
7.1.1	Clinical Studies Used to Evaluate Safety	20
7.1.2	Adequacy of Data	21
7.1.3	Pooling Data Across Studies to Estimate and Compare Incidence	21

7.2	Adequacy of Safety Assessments .....	21
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations .....	21
7.2.2	Explorations for Dose Response.....	22
7.2.3	Special Animal and/or In Vitro Testing.....	22
7.2.4	Routine Clinical Testing.....	22
7.2.5	Metabolic, Clearance, and Interaction Workup .....	23
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class .....	23
7.3	Major Safety Results .....	23
7.3.1	Deaths .....	23
7.3.2	Nonfatal Serious Adverse Events .....	26
7.3.3	Dropouts and/or Discontinuations .....	27
7.3.4	Significant Adverse Events .....	28
7.3.5	Submission Specific Primary Safety Concerns .....	31
7.4	Supportive Safety Results .....	32
7.4.1	Common Adverse Events .....	32
7.4.2	Laboratory Findings .....	34
7.4.3	Vital Signs .....	36
7.4.4	Electrocardiograms (ECGs).....	36
7.4.5	Special Safety Studies .....	36
7.4.6	Immunogenicity.....	36
7.5	Other Safety Explorations .....	37
7.5.1	Dose Dependency for Adverse Events .....	37
7.5.2	Time Dependency for Adverse Events .....	37
7.5.3	Drug-Demographic Interactions .....	37
7.5.4	Drug-Disease Interactions .....	37
7.5.5	Drug-Drug Interactions.....	38
7.6	Additional Safety Explorations .....	38
7.6.1	Human Carcinogenicity.....	38
7.6.2	Human Reproduction and Pregnancy Data.....	38
7.6.3	Pediatrics and Effect on Growth.....	38
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	38
7.7	Additional Submissions.....	38
8	POSTMARKETING EXPERIENCE .....	46
9	APPENDICES.....	46
9.1	Literature Review/References .....	46
9.2	Labeling Recommendations .....	46
9.3	Advisory Committee Meeting .....	46



weight categories. The reader is referred to the Medical Officer's review of the original submission for details of the efficacy data from these trials.

The Complete Response included safety data through Week 100 from C0743T09 and through Week 24 for C0743T12 (ACCEPT). The most common adverse event in both trials was nasopharyngitis, and this was also the case with data through Week 12 for C0743T09 provided in the original submission. In the reviewer's opinion, in neither trial did the data reveal a worrisome pattern or frequency of adverse drug reactions over time. It should be noted that the data from C0743T09 reflected an additional 48 weeks of follow-up since the 120-Day Safety Update (data from C0743T12 reflected an additional 12 weeks of follow-up). No new safety concerns were raised from review of the data submitted in the Complete Response.

The reader is also referred to the Medical Officer's review of the original submission for additional discussion of the risk-benefit assessment and other information pertaining to this application.

### **1.3 Recommendations for Postmarketing Requirements**

The Agency has determined that only clinical trials will be sufficient to assess the risk of serious infection and malignancy with use of ustekinumab. The applicant must implement and/or adhere to their proposed plans for pharmacovigilance activities as below:

1. Continue the treatment of patients enrolled in the pivotal Phase 3 trials PHOENIX 1 (C0743T08) and PHOENIX 2 (C0743T09) for a total of 5 years.

Safety assessments at each scheduled visit should at a minimum include:

- Vital signs
- Evaluation for tuberculosis
- Routine laboratory testing (chemistry and hematology)
- Concomitant medication and adverse event review
- Testing for antibodies to ustekinumab

At a minimum, the following additional evaluations should be performed:

- Pre-injection ustekinumab serum levels should be obtained for pharmacokinetic analysis at each scheduled visit.
- Complete physical examinations (including skin) should be performed at least annually.

2. PSOriasis Longitudinal Assessment and Registry

The PSOriasis Longitudinal Assessment and Registry (PSOLAR; study C0168Z03) is ongoing for infliximab, and patients treated with ustekinumab should be added when appropriate. It is based in North America and designed to collect data on psoriasis patients eligible to receive systemic therapies, including generalized phototherapy and biologics. It is intended to track adverse events in approximately 8,000 patients, and the applicant has previously projected that 4,000 of these patients will have been exposed to ustekinumab.

The registry will actively collect all serious adverse events and other targeted adverse events (malignancies, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, congestive heart failure, hepatotoxicity, and hematologic events). The registry should also include diverticulitis as a targeted adverse event. The registry will also collect data on disease activity and on pregnancy outcomes. The applicant anticipates that the registry will last 8 years from the enrollment of the last subject.

3. The applicant should establish a U.S.-based prospective, observational pregnancy exposure registry that compares the pregnancy and fetal outcomes of women exposed to ustekinumab during pregnancy to an unexposed control population. Outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life.
4. The applicant should conduct a lactation study in women who are breastfeeding while exposed to ustekinumab. This study may be conducted in a subset of women enrolled in the U.S.-based pregnancy registry, who choose to breastfeed their infants and is intended to assess for the presence of ustekinumab in breast milk and potential effects in nursing infants.
5. The applicant should submit data analyses from the Nordic Database Initiative annually for the duration of the study.

The Nordic Database Initiative (NDI) is a proposed prospective, 5+year extendable study of adverse events in all psoriasis patients in Sweden treated with ustekinumab in actual clinical practice. Per the applicant, Sweden has several healthcare databases that together capture information on all persons living there. The applicant intends to combine the data from these registers into one analytical data set, and the applicant states this will capture all psoriasis patients in Sweden and provide the denominator for comparison of adverse events of interest. Per the applicant, the data set would allow for several comparisons, including by disease and indication and with or without ustekinumab exposure. They ultimately expect to follow approximately 4,000 ustekinumab patients for at least 10 years; however, the number of patients in the data set will be a function of both the number of moderate to severe psoriasis patients in Sweden and the uptake of ustekinumab.

The applicant will query these data sets for adverse events of special interest, such as malignancies, infections, cardiovascular events, and deaths over the entire national populations that can include Sweden and other northern European countries. These analyses will be compared where relevant with outcomes from a disease/agent-specific registry based in North America.

6. The applicant should submit data analyses from the Pregnancy Research Initiative (study C0168T71) annually for the duration of the initiative.

This initiative is ongoing in Sweden and Denmark for infliximab and patients treated with ustekinumab exposure should be added when appropriate. It is a prospective, 5-year observational study of pregnancy outcomes in pregnant women with exposure to ustekinumab in actual clinical practice, and of the health status of their infants during a one-year follow-up period. This will be a current exposure-based cohort study in which women with diseases of interest but without prenatal ustekinumab exposure, and their infants, will serve as controls.

7. The applicant should defer evaluation of ustekinumab in pediatric subjects pending analyses of safety data from adults in the trials C0743T08 (PHOENIX 1) and C0743T09 (PHOENIX 2) and the PSOLAR registry once completed. These safety analyses must establish that there are no safety issues that would preclude study of pediatric subjects. Pediatric studies should not be undertaken until there is agreement with the Agency on the design of such studies.

#### **1.4 Recommendations for other Post Marketing Study Commitments**

The following are recommendations for Post Marketing Study Commitments:

1. The applicant should further evaluate maintenance dosing (e.g. longer intervals, lower doses).
2. The applicant should develop an immunogenicity assay that can measure anti-drug antibodies (ADA) in the presence of levels of Stelara expected to be present in patients' serum at the time of ADA sampling. This new assay should be used to assess ADA in patient samples banked from the pivotal trials and/or to assess ADA in on-going clinical trials.
3. The applicant should conduct an in vitro study or studies to determine whether IL-12 and/or IL-23 modulate CYP enzyme expression and whether ustekinumab is able to reverse the effects of IL-12/IL-23 on CYP expression (e.g., in vitro hepatocyte study). An alternative in vivo approach would be to determine the potential of ustekinumab for the alteration of CYP substrate metabolism in psoriasis patients (e.g., a cocktail study with CYP probe drugs).

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

See Medical Officer's review of original submission.

### **2.2 Tables of Currently Available Treatments for Proposed Indications**

See Medical Officer's review of original submission.

### **2.3 Availability of Proposed Active Ingredient in the United States**

The active ingredient has not been approved in the United States.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

See Medical Officer's review of original submission.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

The application was initially submitted on November 28, 2007. A Complete Response letter was issued on December 18, 2008 because of product quality and clinical deficiencies.

Pertaining to the product quality deficiencies, the Complete Response letter conveyed that numerous drug product lots had failed the visible particulate matter assay specification at release and during stability testing, and the application lacked documentation of a reasonable cause of the visible particulate assay out-of-specification (OOS) results. Additionally, the application lacked an accurate testing and sampling method for measurement of visible particulate matter. The applicant was required to identify the root cause of the OOS results and to outline corrective actions to ensure consistent product manufacture and testing. The applicant was also to develop and validate a sampling and testing method for assessment of the level of visible particulates.

Pertaining to the clinical deficiency, the Complete Response letter conveyed that a Risk Evaluation and Mitigation Strategy (REMS) was necessary to ensure that the benefits of Stelara (ustekinumab) outweigh the risks of serious infections and malignancy (including theoretical concerns of vulnerability to particular infections and heightened risk for malignancy from blockade of IL-12/IL-23). Additionally, postmarketing clinical trials would be needed to further assess these risks.

The proposed REMS must contain a

3. a Medication Guide
4. a communication plan that must provide for the dissemination of information about the potential risks of serious infection and malignancy. The communication plan must at minimum include:
  - Dear Healthcare Provider Letters
  - an intensive adverse event reporting awareness campaign,

- a description of the audience for the communication plan,
- a schedule for when and how these letters/materials are to be distributed to healthcare providers at the time STELARA (ustekinumab) is approved, and at specified intervals thereafter, if this application is approved.

Additionally, the proposed REMS must include a timetable for assessment of the REMS that shall be no less frequent than by 18 months, by 3 years and in the 7th year after the REMS is approved.

### **Applicant's Complete Response**

With regard to the product quality deficiencies, the applicant submitted:

- a root cause investigation for the OOS results for the visible particulate assay, which, per the applicant, identified the root cause for the OOS results
- a sampling and testing method for the assessment for the level of visible particulates in the drug product with supporting documentation.

With regard to the clinical deficiency, the applicant submitted a proposed REMS consisting of two parts:

- the proposed REMS itself, consisting of a Medication Guide, a communication plan, and a timetable for assessment and
- a REMS supporting document which was said to provide a rationale for each of the elements in the proposed REMS.

The submission also included a safety update and revised labeling.

## **2.6 Other Relevant Background Information**

Since the original submission date, the product has received approval from the Canadian Health Authority (Health Canada) and by the European Medicines Agency (EMA).

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

#### **Medical Officer's Review of the Proposed REMS**

The proposed REMS as initially provided in the Complete Response submission was insufficiently detailed, and the applicant was requested to submit a revised, more comprehensive document. This review will not provide comments on all elements of each revised proposed REMS submitted in response to Information Requests (there were several). The reviewer's comments will largely be limited to the proposed REMS initially submitted in the applicant's Complete Response, the revised proposed REMS submitted April 10, 2009 (the first revised

proposed REMS that began to provide the necessary level of detail) and the revised proposed REMS submitted June 26, 2009.

As previously stated, the Complete Response letter informed the applicant that the proposed REMS must contain:

- a Medication Guide
- a communication plan
- a timetable for assessments.

In the Complete Response letter, the Agency also suggested that the proposed REMS submission include two parts: the proposed REMS itself and a REMS Supporting Document. The following discussion describes the applicant's proposals for addressing the required elements of the REMS and provides for the reviewer's assessment of the applicant's proposals.

The Division of Risk Management (DRISK) also reviewed the proposed REMS and supporting document. The final DRISK risk consult was pending when the clinical review closed; therefore, the conclusions regarding the adequacy of the REMS are the Medical Officer's and should be considered preliminary pending completion of the DRISK consult. An addendum will be added to the clinical review on completion of the DRISK consult.

#### Medication Guide

Per the Complete Response letter, "STELARA (ustekinumab) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of STELARA (ustekinumab)." In addition to being appended to the package insert, the applicant (and/or its affiliates) proposes to provide the Medication Guide itself or the means to produce the document to "distributors, packers, or authorized dispensers" for distribution to patients who receive a prescription for ustekinumab. The applicant will also make the Medication Guide available on the STELARA™ websites (patient and professional).

The draft Medication Guide did not include mention of the theoretical risks from IL-12/IL-23.

---

The Office of Surveillance and Epidemiology review of the Medication Guide was pending as the clinical review closed.

#### Communication Plan

The applicant initially proposed a communication plan to comprehensively target dermatologists, and health care providers likely to prescribe and/or administer ustekinumab. Communication with rheumatologists and oncologists would be limited to the adverse event awareness campaign and continuing medical education (CME) portions of the communication plan. This proposed approach was not sufficiently broad, as it would not have adequately addressed practitioners who might see patients with complications associated with treatment, e.g. the Healthcare Providers Letters would be distributed only to practitioners of dermatology. Additionally, the target audience did not include certain other practitioners who might see complications of treatment e.g. infectious disease specialists.

The Complete Response letter conveyed that the communication plan must include the four elements presented in bold below (quoted from the Complete Response letter). Following each

b(4)

bolded quote are the applicant's proposals for addressing each of the four required elements and the reviewer's assessment of the applicant's proposals.

**"1. Dear Healthcare Provider Letters to be distributed to dermatologists and other specialties expected to use STELARA (ustekinumab), chronically to treat psoriasis, if the application is approved, to provide information about complications potentially associated with STELARA (ustekinumab). This letter should also inform healthcare providers about any available registries that may enroll patients treated with STELARA (ustekinumab)."**

The applicant proposed to distribute a Dear Healthcare Provider Letter with the package insert (including Medication Guide) to the target audience which, for this element of the communication plan, the applicant defined only as practitioners of dermatology. These materials would also be available on the STELARA<sup>®</sup> professional website. The applicant would also distribute Dear Pharmacist Letters.

The applicant appended draft letters to the proposed REMS provided in the initial submission of their Complete Response. These letters were somewhat generic in that they provided information that could apply to any immunosuppressant and lacked content that addressed the theoretical concerns that might attach to IL-12/IL-23 blockade. Additionally, the draft letters included irrelevant discussion of clinical trial data. Appropriately, the draft Dear Healthcare Provider Letter provided in the initial submission of the Complete Response encouraged adverse event reporting and advised of the PSOLAR registry (although in a limited fashion).

In response to an Information Request, on June 26, 2009, the applicant submitted a revised draft letter. The revised document was more specific to ustekinumab, in that it included mention of the theoretical risks from IL-12/IL-23 blockade (although the discussion could probably be expounded). Additionally, the applicant appropriately deleted the discussion of the clinical trial data. The document also encouraged reporting of adverse events and provided the methods for so doing. Lastly, the document advised of the PSOLAR registry. In the reviewer's opinion, this revised document was generally acceptable.

**"2. An intensive adverse event reporting awareness campaign at major national meetings of appropriate specialties; if possible, develop and provide free-of-charge targeted CME programs covering the basic science underlying recommendations about infectious complications and the need for cancer surveillance."**

The applicant initially proposed to conduct an intensive adverse event reporting awareness campaign at major national meetings of dermatologists, rheumatologists and oncologists. The applicant would also attempt to develop and provide CME programs free-of-charge to educate on "the basic science underlying the recommendations about infectious complications and the need for cancer surveillance." The applicant initially provided no details of the intensive adverse event reporting awareness campaign. Aside from naming the specialties that would be targeted, they essentially just restated this element of the communication plan from the Complete Response letter.

In an Information Request sent to the applicant on February 23, 2009, the Agency requested details of the adverse event reporting awareness campaign for each specialty and that the applicant describe the goals for each specialty. The applicant responded in a submission with

letter date March 5, 2009. In this submission, they had modified the campaign to focus on dermatologists at major national scientific meetings, e.g. the annual and summer meetings of the American Academy of Dermatology. They no longer intended to target rheumatologists or oncologists in the campaign.

The submission included a sample of “campaign content” that could serve as the basis for other materials to be used in the campaign (e.g. panel boards, brochures, etc.) and some details of their proposed outreach efforts at scientific meetings. However, the submission did not include any of the other materials (i.e. panel boards, brochures, etc.), and these materials would require Agency review as they would be part of the REMS.

The sample of campaign content provided in the March 5<sup>th</sup> submission was a two-page document, much of it in question-answer format. The document included promotional statements, irrelevant discussion of clinical trial data and discussion of risks that could apply to virtually any immunosuppressant. However, it also included some discussion of theoretical risks that might attach to ustekinumab specifically, e.g. recurrent salmonella infections and the science underlying the concern regarding the theoretical risks. It also included information about the MedWatch Reporting System.

In the submission with letter date April 10, 2009, the applicant redefined the proposed primary audience for the communication plan as oncologists, infectious disease specialists, gastroenterologists, rheumatologists, and dermatologists. Also, this submission included drafts of educational materials (e.g. poster boards, journal ads) proposed for each of the target specialties. The applicant also described their plans to partner with professional societies to develop additional measures for educating their members on theoretical risks and included drafts of letters to various societies. (Note: These letters would not be part of the REMS, as they are not for distribution to prescribers). The applicant described their intentions to encourage patient participation in the PSOLAR registry and that physicians refer patients to PSOLAR investigative sites. The submission included a description of the applicant’s plans to develop a REMS website and a draft of their Request for Proposal for development of accredited educational activities.

The April 10<sup>th</sup> submission was the first to provide drafts of the content of assorted proposed educational materials, e.g. service announcements for each specialty in the target audience. Although the submission provided for more comprehensive content, the assorted documents continued to include:

- promotional statements, e.g. “Centocor Ortho Biotech Inc.’s dedication to patient safety includes long-term commitment to clinical trials...”
- discussion of information from the clinical trials not relevant to the REMS, e.g. “In controlled studies of psoriasis patients receiving STELARA™, the rates of infection, serious infection and malignancy were similar between patients treated with STELARA™ and the placebo-control group.”

The submission also included information appropriate for the REMS and consistent with the requirements detailed in the Complete Response letter. Examples follow:

- “Based on data from rodent models, there is a potential concern that blockade of IL-12 and IL-23 may heighten patients’ risk for malignancies.”
- “Reporting adverse events after drug approval is important to help Centocor Ortho Biotech Inc. and the Food and Drug Administration (FDA) understand the safety profile of STELARA™...”

The submission also included a screen-shot of the home page for the proposed REMS web page, and listed items which would be housed on the web page, e.g. the Medication Guide, the Dear Healthcare Provider Letter. However, the text for the home page itself was not submitted. A revised screen-shot, submitted June 26, 2009, provided draft content of the home page itself.

There was no mention of theoretical concerns from IL-12/IL-23 blockade. Additionally, the screen-shot provided select information from the label that would not be supportive of the REMS, e.g. the most common adverse reactions in the clinical trials.

The applicant submitted revised draft service announcements on June 26, 2009. The revised documents no longer contained promotional content or discussion of clinical trial data. The message appropriately focused on the science underlying the theoretical concerns from use of ustekinumab and advised of how to report adverse events. Additionally, the service announcements were appropriately revised to be "specialty-specific", e.g. the service announcement for oncologists described that data from rodent models was the basis for the theoretical concerns for heightened risk of malignancy.

**"3. A description of the audience for the communication plan, stating specifically the types and specialties of healthcare providers to whom the communication materials will be directed. These should include non-prescribers in specialties likely to be consulted for infectious or malignant adverse events."**

In the submission with letter date April 10, 2009, the applicant defined the primary audience for the communication plan as oncologists, infectious disease specialists, gastroenterologists, rheumatologists, and dermatologists (it had been defined otherwise in previous submissions during the review cycle). This target audience is acceptable as it includes those likely to prescribe the product and those who might see complications associated with use of the product.

**"4. A schedule for when and how these letters/materials are to be distributed to healthcare providers at the time STELARA (ustekinumab) is approved, and at specified intervals thereafter, if this application is approved."**

The applicant proposes to distribute the letters, Medication Guide and the professional label at approval, and 6, 12, 18, and 36 months thereafter. This proposal is reasonable in the reviewer's opinion.

#### Timetable for Submission of Assessments

The REMS assessment will be submitted to the Agency FDA within 60 days of the close of the interval in accordance with the following schedule:

<u>Assessment Submission</u>	<u>Timing Interval Relative to Approval</u>
1st Assessment	18 months after approval
2nd Assessment	3 years after approval
3rd Assessment	7 years after approval

This schedule is consistent with the minimal frequency outlined in the Complete Response letter.

### **REMS Supporting Document**

The Complete Response letter suggested that the REMS submission include a supporting document. This document should be a document explaining the rationale for each of the elements included in the proposed REMS...”

#### **Background (Section 1)**

The Background section included a discussion of the bases for the theoretical concerns associated with ustekinumab use. The statement is similar to the stated clinical deficiency in the Complete Response letter. The Background section is then divided into two sub-parts one each devoted to discussion of the two categories of potential/theoretical risks in the context of ustekinumab use (i.e. malignancy and serious infections and the theoretical heightened risk of malignancy based on rodent data and the theoretical risk of susceptibilities/vulnerabilities to particular serious infections based on events in humans who are genetically deficient in IL-12/IL-23).

#### **Malignancy (Section 1.1)**

In the reviewer’s opinion, rather than presenting some of the scientific data that provide the basis for the theoretical concern regarding malignancy, the applicant was more focused on why such data (again not presented) may not be relevant to patients treated with ustekinumab. The applicant also included an overview of the malignancy data from the safety database of the Phase 3 studies, and these data do not provide a rationale for any element of the REMS.

In the reviewer’s opinion, the tone and content of this section of the document were reminiscent of the position paper included in the Enhanced Risk Management Plan submitted after the Advisory Committee meeting (see Medical Officer’s review of the original submission). The discussion provided limited rationale for this element of the REMS and more served to present counter arguments to the theoretical concern regarding malignancy.

#### **Serious Infections (Section 1.2)**

In the reviewer’s opinion, this section provides adequate rationale for the REMS. The section includes discussion of theoretical concerns about specific types of infections (including serious infections) that might attach to ustekinumab use. The applicant discusses animal data and humans genetically deficient in the cytokines of interest.

#### **Goal (Section 2)**

The goal of the REMS is stated as being “...to seek to ensure that the benefits of the drug outweigh the potential risks of serious infection and malignancy.” This is acceptable and consistent with wording in the Complete Response letter.

#### **Additional Potential Elements (Section 3.1)**

This section discusses the elements of the REMS, i.e. the Medication Guide, communication plan and the Dear Healthcare Professional Letter and is generally acceptable.

### 3.2 Compliance with Good Clinical Practices

See the Medical Officer's review of the original submission.

### 3.3 Financial Disclosures

See the Medical Officer's review of the original submission.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

To address the product quality deficiencies, the applicant was required to identify the root cause of the OOS results and to outline corrective actions to ensure consistent product manufacture and testing. Additionally, the applicant was to develop and validate a sampling and testing method for assessment of the level of visible particulates. The Medical Officer's understanding of the product quality issues follows and is intended as an overview. The reader is referred to the product quality review for the definitive, detailed discussion of these issues.

Prior to the Complete Response action, the applicant suggested that \_\_\_\_\_ used for \_\_\_\_\_ the quality control visible particle assay \_\_\_\_\_ and that the particles were therefore artifacts of \_\_\_\_\_. Investigations revealed that the particles were not \_\_\_\_\_. The applicant proposed changing to glass syringes \_\_\_\_\_ in the assay as a solution to the OOS results. The product quality reviewer recommended a Complete Response action in part because a root cause for the OOS results had not been determined (although, as stated, the applicant believed the results were due to \_\_\_\_\_. In their Complete Response (and in a response to an Information Request), the applicant included data to support that the \_\_\_\_\_ were indeed the root cause of the OOS results. The applicant had modified the assay to use glass syringes and provided data from the modified assay to support that this change would provide a reliable sampling method.

b(4)

Stability data at recommended storage temperature received in August 2008, suggested an increased rate of translucent visible particles at 4°C in each successive drug product lot. While there were no stability failures, the applicant's trending analysis revealed that validation batches would not meet the proposed \_\_\_\_\_ shelf-life. These findings prompted an out-of-trend (OOT) investigation of the differences between the clinical lots and validation lots. The visible particles were found to contain \_\_\_\_\_ and were of the same composition as those formed in the drug product under stressed/accelerated conditions (but of different composition

b(4)

than particles that prompted the OOS investigations). The \_\_\_\_\_ reflected normal degradation. The \_\_\_\_\_ suggested possible \_\_\_\_\_ be definitively determined. It is thought that that increased degradation in the validation batches compared to the clinical batches might have been enhanced by the \_\_\_\_\_ used for the assay. The applicant's proposals to address the OOT results, included changing the shelf-life to 12 months, changing the release specification to category B, and continuing the OOT root cause investigation. The product quality reviewer concluded that commitments made by the applicant should "adequately address safety concerns."

b(4)

The commercial acceptance criterion was for particles to be  $\leq C$  at release. Per the applicant's response to an Information Request (submission date May 1, 2009), samples taken from clinical batches (both 45mg and 90 mg) had particle categories from B to D (45mg) and C to D (90mg). This submission included analyses comparing safety and efficacy outcomes for subjects who received product with visible particulate levels  $\geq C$  to those who received product with levels of  $< C$  ( $\leq B$ ). See Section 7.7 of this review.

#### **4.2 Clinical Microbiology**

The product is not an antimicrobial.

#### **4.3 Preclinical Pharmacology/Toxicology**

See the Medical Officer's review of the original submission.

#### **4.4 Clinical Pharmacology**

##### **4.4.1 Mechanism of Action**

See the Medical Officer's review of the original submission.

##### **4.4.2 Pharmacodynamics**

See the Medical Officer's review of the original submission.

##### **4.4.3 Pharmacokinetics**

See the Medical Officer's review of the original submission.

### **5 Sources of Clinical Data**

#### **5.1 Tables of Clinical Studies**

See discussion of studies in Section 5.3

## 5.2 Review Strategy

See Section 7.

## 5.3 Discussion of Individual Studies

The applicant submitted data from three studies:

1. C0743T09
2. C0743T12
3. C0743T10

### **C0743T09 (T09; PHOENIX 2): A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Evaluating the Efficacy and Safety of Ustekinumab (CNTO 1275) in the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis**

This ongoing Phase 3 trial is one of the pivotal trials and is intended to continue through Week 264 (five years). The applicant provided data through Week 52 in the 120-day Safety Update, and the Complete Response provided for data through Week 100. This trial is now in the long-term extension phase (which continues through Week 264). The long-term extension began at Week 52, at which point all subjects began receiving ustekinumab. Subjects who entered the long-term extension phase of the trial will continue to receive the same dose and schedule of ustekinumab that they were receiving at Week 52. The trial remained blinded until all subjects completed the Week 52 visit and the Week 52 database was locked. After the unblinding, dose interval adjustment (from every 12 weeks to every 8 weeks) or dose escalation (from 45mg to 90mg) is allowed at the investigator's discretion. Subjects who continued dosing every 12 weeks received treatment at Weeks 64, 76, and 88. Subjects whose dosing interval was increased to every 8 weeks received treatment at Weeks 60, 68, 76, and 84.

Subjects had follow-up generally every 4 weeks through Week 52. Follow-up will generally be every 12 weeks during the long-term extension phase (i.e. after Week 52).

### **C0743T12 (T12;ACCEPT): A Phase 3, Multicenter, Randomized Study Comparing CNTO 1275 and Etanercept for the Treatment of Moderate to Severe Plaque Psoriasis**

This Phase 3 trial is ongoing and is intended to continue through Week 64. This trial enrolled subjects with moderate to severe psoriasis, who had an inadequate response to, were intolerant to, or had a contraindication to cyclosporine, methotrexate (MTX) or psoralen plus ultraviolet A light (PUVA). The primary objective of this trial was to compare the efficacy of ustekinumab to etanercept and evaluate the safety of ustekinumab and etanercept in the treatment of subjects with moderate to severe plaque psoriasis. The primary endpoint was the proportion of subjects who achieved a PASI 75 response at Week 12. The applicant provided data through Week 12 in the 120-day Safety Update. The Complete Response provided for data through Week 24.

After Week 12, subjects who remained in the study received (or are to receive) treatment as below:

- Week 12 PGA responders ( $PGA \leq 2$ ) who experienced recurrence of psoriasis at or prior to Week 40 were retreated with their original dose of ustekinumab (if randomized to ustekinumab dose groups) or with ustekinumab 90 mg (if randomized to etanercept group) at the visit when the recurrence of psoriasis occurs and 4 weeks later.
- Week 12 PGA nonresponders received their original dose of ustekinumab (if randomized to ustekinumab dose groups) at Week 16, or ustekinumab 90mg (if randomized to etanercept group) at Weeks 16 and 20.

Note: The PGA was a composite score mathematically-derived from the assessment of induration, erythema and scaling.

Prior to Week 12 (i.e. Weeks 0 through 12), subjects were dosed as below:

Group 1: Ustekinumab 45 mg at Weeks 0 and 4

Group 2: Ustekinumab 90 mg at Weeks 0 and 4

Group 3: Etanercept 50 mg twice weekly through Week 12.

### **C0743T10**

The applicant conducted a randomized, double-blind, placebo-controlled Phase 2 study which evaluated ustekinumab for treatment of psoriatic arthritis. Subjects were followed through Week 36, and there were two dosing groups:

- Group 1: 90 (or 63) mg of ustekinumab SC at Weeks 0, 1, 2, 3 and placebo at Weeks 12 and 16
- Group 2: 90 (or) 63 mg of placebo SC at Weeks 0, 1, 2, 3 and ustekinumab at Weeks 12 and 16.

This study had been completed by the time of submission of the 120-day Safety Update. See Section 7.1.1 for additional comment on this study.

## **6 Review of Efficacy**

### **Efficacy Summary**

#### **6.1 Indication**

##### **6.1.1 Methods**

See the Medical Officer's review of the original submission and Section 6.1.10 of this review.

##### **6.1.2 Demographics**

See the Medical Officer's review of the original submission.

### 6.1.3 Patient Disposition

See the Medical Officer's review of the original submission and Section 6.1.10 of this review.

### 6.1.4 Analysis of Primary Endpoint(s)

See the Medical Officer's review of the original submission.

### 6.1.5 Analysis of Secondary Endpoints(s)

See the Medical Officer's review of the original submission and Section 6.1.10 of this review.

### 6.1.6 Other Endpoints

See the Medical Officer's review of the original submission.

### 6.1.7 Subpopulations

See the Medical Officer's review of the original submission.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See the Medical Officer's review of the original submission.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See the Medical Officer's review of the original submission.

### 6.1.10 Additional Efficacy Issues/Analyses

The EMEA requested inspection of an investigational site in Canada as the investigator had not conducted the global assessment in accordance with the protocol. Specifically, this investigator based his global evaluation on his clinical assessment of overall disease status, a more appropriate way to assess global status in the reviewer's opinion, rather than the mathematically-derived assessment called for in the protocol. (Note: The applicant apparently did not submit the scale for Agency review/comment until after the Phase 3 trials were underway; the Agency would not have agreed to a derivative global scale).

Per the statistical review of the applicant's Complete Response done by Dr. Fritsch, "(a)fter the EMEA inspection, the applicant updated the datasets using information from the original source data so that the PGA scores from this investigator reflected the intent of the protocol. The use of the modified PGA scores does not alter the efficacy conclusions of Studies 08 and 09, which demonstrated that ustekinumab is effective in the treatment of psoriasis."

The modified PGA had little to no impact on PGA outcomes, with rates of success remaining essentially the same as under the original analyses. The original and modified PGA success rates

are presented in the table below from the statistical review. Dr. Fritsch stated in her review that the modified Week 12 PGA results may be used in labeling, and the Medical Officer agrees.

**Table 1 from the Statistical Review**

	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
<b>Study 08</b>	N=255	N=256	N=255
Original	154 (60%)	158 (62%)	10 (4%)
Modified	151 (59%)	156 (61%)	10 (4%)
<b>Study 09</b>	N=409	N=411	N=410
Original	278 (68%)	302 (73%)	20 (5%)
Modified	277 (68%)	300 (73%)	18 (4%)

## 7 Review of Safety

### Safety Summary

#### 7.1 Methods

##### 7.1.1 Clinical Studies Used to Evaluate Safety

New safety data were submitted from two ongoing studies (discussed further below; also see Section 5.3):

1. C0743T09 (T09; PHOENIX 2): data through Week 100
2. C0743T12 (T12; ACCEPT): data through Week 24

The Complete Response included the following data for these studies:

- Serious adverse events
- Adverse events leading to discontinuation of study agent
- Common adverse events
- Updated exposure numbers.

The applicant also included data through Week 36 for study C0743T010 (T10). This study evaluated ustekinumab in the treatment of psoriatic arthritis. Study T10 had been completed when the 120-Day Safety Update was submitted (April 4, 2008). The applicant included some information about serious adverse events that occurred in this study in the 120-Day Safety Update (including the one serious infection of respiratory tract infection in a subject who had received two doses of ustekinumab), and these have been previously discussed in the Medical Officer's review of the original submission. The 120-Day Safety Update also described the one malignancy that was reported in the ustekinumab group through Week 36 (basal cell carcinoma) and also included some information regarding injection site reactions. The 120-Day Safety Update provided limited discussion of discontinuations due to adverse events and common

adverse events. The Complete Response provided for details and/or presentations not included in the Safety Update: tabulations of serious adverse events (brief narratives were provided in the Safety Update), discontinuations due to adverse events and common adverse events. This trial will not be further addressed in this review, as the serious adverse events were described in the Medical Officer's review of the original submission.

The applicant did not provide new safety information for the other ongoing Phase 3 trial C0743T08 (T08; PHOENX 1) in the safety update submitted in the Complete Response, as no database lock had occurred for this trial since the 120-Day Safety Update. In response to an Information Request, the applicant submitted a summary of serious adverse events in T08 that occurred post-database lock for the 120-Day Safety Update (see Section 7.7).

### 7.1.2 Adequacy of Data

The data were reviewable.

### 7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Data from T09 and T12 were not pooled because of the differences in study designs (See Section 5.3) and the differences in collection of safety data. In T09, collection of adverse event data was by query at the investigative site; in T12 collection of these data was via subject diaries (in which subjects were to daily record any events).

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The Complete Response provided for approximately an additional 12 months of exposure of 1,212 subjects to ustekinumab (45mg and 90mg combined) in study T09 since the 120-Day Safety Update. The submission provided for an additional 6 months of exposure to ustekinumab from T12 for 556 subjects who were randomized to ustekinumab treatment at baseline and approximately 7 weeks of exposure for subjects who crossed over from etanercept treatment to ustekinumab.

**Applicant Table 8 Summary of duration of follow-up and exposure through Week 100; ustekinumab-treated subjects in C0743T09**

	Ustekinumab		
	45 mg <sup>a,b</sup>	90 mg <sup>a</sup>	Combined
Subjects treated	606	606	1212
Avg duration of follow-up (weeks)	87.58	88.99	88.28
Avg exposure (weeks)	77.37	78.11	77.74
Avg number of ustekinumab administrations	8.7	8.6	8.6

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

<sup>b</sup> Subjects randomized to 45 mg who had a dose escalation to 90 q8 wks are included in the 45 mg group.

**Applicant Table 7: Summary of duration of follow-up and exposure through Week 24; ustekinumab-treated subjects in C0743T12**

	<u>45 mg</u>	<u>90 mg</u>	<u>Ustekinumab Only</u>	<u>Etanercept → 90 mg</u>	<u>Combined Ustekinumab<sup>a</sup></u>
Treated subjects	209	347	556	197	753
Avg duration of follow-up (weeks)	23.7	24.0	23.9	6.7	19.4
Avg exposure (number of administrations)	2.3	2.3	2.3	1.6	2.1

<sup>a</sup> Includes subjects randomized and treated with ustekinumab and those who were treated with ustekinumab after crossing over from etanercept.

### 7.2.2 Explorations for Dose Response

Data presentations included presentations by treatment group, i.e. those who received 45mg and those who received 90mg of ustekinumab.

### 7.2.3 Special Animal and/or In Vitro Testing

See the Medical Officer's review of the original submission.

### 7.2.4 Routine Clinical Testing

See Section 7.4.2.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

See the Medical Officer's review of the original submission.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

This product is first-in-class.

## 7.3 Major Safety Results

### 7.3.1 Deaths

The applicant reported 10 deaths in the development program, five of which have been previously reported to the BLA (in the original submission and 120-day Safety Update). Five deaths have been reported since the 120-day Safety Update:

#### C0743T08-007-011

This subject was a 50 y/o female with a history of seizure disorder and alcohol and intake who was diagnosed with pneumonia, pancreatitis, petit mal seizure, and urinary tract infection on Day 61 prior to receiving ustekinumab (received placebo at Day 1/Week 0 and Day 28/Week 4). She was hospitalized on Day 61 / ██████████ for the adverse event of petit mal epilepsy and was diagnosed with the serious adverse event of pneumonia the day after admission. She was discharged on ██████████ (Day 65), and all events were reported to be resolved on that date. She received 90 mg of ustekinumab Day 94/Week 12, Day 119/ Week 16 and Day 199/Week 28. She was randomized to the withdrawal group at Week 40, and ustekinumab was reinitiated at Week 84 (Nov. 20, 2007) with loading doses that week and at week 88 (Dec. 12, 2007). However, she received no additional doses after Week 88 because of elevated liver function tests and concerns that she might have resumed alcohol consumption. She was hospitalized with end-stage liver disease, alcohol withdrawal, hepatic encephalopathy, and seizure disorder, hypoxic respiratory failure, bilateral pneumonia, and colitis on ██████████ (approximately 9 to 10 months after last dose of ustekinumab). She was transferred to hospice care the same day and died the following day ██████████. The causes of death included hypoxic respiratory failure, bilateral pneumonia, end-stage liver disease and colitis. An autopsy was not performed.

b(6)

#### C0743T08-202-002

This subject was a 42 y/o male who received 90mg of ustekinumab on Day 29/Week12, Day 113/Week 12, Day 211/Week 28 (June 12, 2006, July 11, 2006 and October 17, 2006). He had received placebo at Weeks 0 and 4. He committed suicide on ██████████. No autopsy was performed.

#### C0743T09-005-016

This subject was an 80 y/o female received placebo at weeks 0 and 4. She received eight doses of ustekinumab 45 mg on Day 83/Week 12 through Day 623/Week 88 (Feb. 12, 2008).

She had a history of hypertension and her body mass index (BMI) was 29.3. This subject also experienced herpes zoster on Day 503 (not a serious adverse event; not treated; resolved Day 529; ustekinumab resumed on Day 533). On October 1, 2008, the subject's daughter informed the investigator that her mother was hospitalized and died on \_\_\_\_\_ due to a heart attack followed by a stroke. An autopsy was not performed. The subject was reportedly taking celecoxib at the time of the myocardial infarction. She had received her last dose of study agent at Week 112 (July 30, 2008), approximately 8 weeks before her death.

b(6)

Subject C0743T12-1018-002

This was a 25 year-old male who received ustekinumab 90 mg (Weeks 0 and 4; July 25 and August 22, 2007, respectively). On \_\_\_\_\_ progressive decrease in motor function of right arm and leg (reported onset February 23, 2008) was reported and resulted in hospitalization. Symptoms had progressed to include inability to write or grasp. He did not have any other neurologic deficits. Emergency room (ER) evaluation revealed (+) 2/5 strength of the right upper extremity (RUE). A computerized tomography (CT) scan of the head revealed "no active bleed/MLS, bilateral MRC versus a polyp." Examination on \_\_\_\_\_ revealed RUE strength of 4/5, but his grip was "2-3/5." He had hyperreflexia on the right side, and sensory was intact. The admitting diagnoses were subacute right arm weakness and possible multiple sclerosis. Findings from a magnetic resonance imaging (MRI) scan of the brain done \_\_\_\_\_ were nonspecific but possibilities included subacute infarction, an evolving encephalitis or a demyelinating process (from review of the MRI report). A cerebrospinal fluid examination on \_\_\_\_\_ revealed no cells or organisms and no growth at 2 days. Fungal cultures and oligoclonal bands were negative. He was discharged on \_\_\_\_\_ on acetylsalicylic acid 81 mg daily with a diagnosis of possible stroke or demyelinating disease and was scheduled for neurology clinic after 3 weeks.

b(6)

On \_\_\_\_\_, he returned to the emergency room with the chief complaint of right lower extremity weakness and gait difficulty for 2 days, and his RUE weakness had progressed. An MRI scan of the brain revealed a lesion in the left posterior frontal lobe with hyperintensity signal diffusion image without mass effect. Differential diagnoses included infarction, neoplasm, vascular malformation or inflammatory adhesion. Cerebrospinal fluid (CSF) studies showed no inflammatory cells or protein invasion and no bands, negative Gram stain, and angiotensin-converting enzyme (ACE) in CSF was normal. He was admitted to the neurology service on \_\_\_\_\_. Physical examination findings included increased motor tone in the right upper and lower extremities, right-sided hemiparesis, and weakness in the right upper and lower extremities (worse in upper).

b(6)

During this hospitalization, the subject's human immunodeficiency virus (HIV) test result was positive and reported as a new serious adverse event with onset date of May 5, 2008. His CD4 lymphocyte count was 14 on May 1, 2008 (units and reference range not provided). Retrospective testing of a stored baseline serum sample revealed that the subject was HIV antibody positive at screening for study enrollment. Also, his absolute lymphocyte count at screening was 0.66 x 10<sup>3</sup>/μL (normal range 1.02-3.36 x 10<sup>3</sup>/μL; CD4+ count not known). An infectious disease consult was obtained. He was prescribed sulfamethoxazole/trimethoprim DS and azithromycin. He also had electroencephalogram (EEG) abnormalities, but no seizure activity. He was discharged on \_\_\_\_\_, in fair condition with discharge diagnoses of probable progressive multifocal leukoencephalopathy (PML) and newly diagnosed HIV.

b(6)

He was hospitalized [redacted] with complaints of progressive weakness, fever, headaches, nausea, and vomiting for 2-3 days. On admission, findings included slurred speech and 0/5 right-sided strength. The admitting diagnosis was likely PML versus lymphoma versus infection. Treatment included prophylactic antibiotics and highly active antiretroviral treatment (HAART). An MRI scan of the brain done [redacted] revealed the left frontoparietal abnormality had enlarged, but the overall findings were nonspecific. However, the report (reviewed by this Medical Officer), closes with the following comment: "The appearance is not particularly suggestive of central nervous system lymphoma, PML or toxoplasmosis." A blood culture grew methicillin-resistant *Staphylococcus epidermidis* (MRSE), which was treated with vancomycin. On [redacted] a lumbar puncture revealed mildly elevated protein in the CSF, normal glucose, and cultures were negative. Jakob-Creutzfeldt (JC) virus and cytomegalovirus (CMV) were negative by polymerase chain reaction (PCR) testing of spinal fluid. He received piperacillin/tazobactam for a possible aspiration pneumonia and fluconazole for a presumed yeast infection (the latter discontinued because of elevated LFTs).

b(6)

A brain biopsy was performed on [redacted]. Stains were negative for *Toxoplasma*; bacteria and fungi were negative, but several cell nuclei were suspicious for PML. Sections sent out for PML staining revealed no immunostaining evidence of PML. From the pathology report reported on June 27, 2008 (reviewed by the Medical Officer):

**Final Pathologic Diagnosis**

LEFT DEEP SUBCORTICAL STEREOTACTIC BIOPSY - SMALL FRAGMENTS OF CEREBRAL TISSUE WITH SEVERAL ROUND, GROUND GLASS-APPEARING NUCLEI THAT ARE LARGER THAN NORMAL OLIGODENDROCYTE NUCLEI, WITH PARTIAL TISSUE LIQUEFACTION BY FOAMY MACROPHAGES, AND MILD GLIOSIS. SOME OF THE ENLARGED ASTROCYTIC NUCLEI ARE VERY LARGE, BUT NOT BIZARRE (SEE COMMENT).

IMMUNOSTAIN FOR TOXOPLASMA IS NEGATIVE, AND BOTH BACTERIAL AND FUNGAL STAINS ARE NEGATIVE.

**Comment**

The biopsy is not diagnostic, and stains for *Toxoplasma*, bacteria and fungi are negative, but there are several cell nuclei suspicious for progressive multifocal leukoencephalopathy (polyomaviral infection). The background of enlarged astrocytic nuclei and foamy macrophages is that expected in a fairly advanced lesion of PML, but the few suspicious nuclei are not diagnostic alone. In PML lesions that are somewhat advanced, few classic ground glass nuclei if any remain. Sections are being sent out for PML staining and an Addendum will be added with the results.

From the addendum reported July 7, 2008:

**Addendum Diagnosis**

LEFT DEEP SUBCORTICAL STEREOTACTIC BIOPSY - NO IMMUNOSTAINING EVIDENCE (NEGATIVE STAINING) FOR PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY.

**Addendum Comment**

Immunostaining (Genzyme Specimen # 08-50797570-MH) is negative for PML virus.

He was found to have a left upper extremity cellulitis on [redacted] and was treated with vancomycin. On the following day, he developed a fever (102.4), hypotension, (systolic blood pressure 50 - 60's), and he became more lethargic. He was treated with IV antibiotics and IV fluids and was transferred to the intensive care unit. That evening, he experienced respiratory distress and was diagnosed with sepsis. The subject received fluid resuscitation and pressor agents and was ultimately intubated. He experienced a 20-minute episode of ventricular tachycardia. He developed acute renal failure on [redacted] (secondary to acute tubular necrosis). He was started on empiric metronidazole for possible *Clostridium*

b(6)

*difficile* diarrhea. Post anoxic encephalopathy was apparently diagnosed on [REDACTED]. He developed disseminated intravascular coagulation and multi-system organ failure. Bronchial cultures were positive for *Escherichia coli*. He experienced atrial fibrillation on [REDACTED]. On [REDACTED] the family agreed to terminal extubation, and he expired the following day. An autopsy was not performed (this was reconfirmed in the applicant's response to an Information Request; submit date: April 27, 2009), and the primary cause of death was not reported.

b(6)

In the reviewer's opinion, the available information does not support that this subject had PML. Even if a diagnosis of PML were to have been established, his HIV status would confound any attribution of causation to ustekinumab.

#### Subject C0743T12-2017-00004

This subject was a 48-year-old female who was treated with etanercept. She was involved in a motor vehicle accident in which she was ejected from the car. She was taken to a hospital where she was pronounced dead.

### 7.3.2 Nonfatal Serious Adverse Events

Nonfatal serious adverse events are discussed below.

#### Serious adverse events study T09 through Week 100

From Appendix A.3, a total of 117 serious adverse events were reported in ustekinumab-treated subjects (9.7%) through Week 100. The proportions of subjects experiencing a serious adverse event were similar between the two dosage groups: 61 (10.1%) in the 45 mg group and 56 (9.2%) in the 90 mg group. "Cardiac disorders" was the system organ classes (SOC) in which serious adverse events were most commonly reported, and 8 events were reported in both dosage groups (1.3% in both groups). The most commonly reported serious adverse event was coronary artery disease: 4 (0.7%) in the 45 mg group; 1 in the 90 mg group. The other events for which there were multiple reports were "angina unstable" [2 (0.3%) in each group] and myocardial infarction [2 (0.3%) in the 45 mg group and 1 (0.2%) in the 90 mg group]. "Injury, poisoning and procedural complications" was the SOC with the second highest number of serious adverse events, and there were single reports of 15 events in similar proportions between groups (1.3% in the 45 mg group and 1.2% in the 90 mg group).

A total of 15 serious adverse events were reported in the "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" SOC, and the proportions were comparable between groups: 6 (1.0%) in the 45mg group and 9 (1.5%) in the 90mg. Of the 15 events, 12 were malignancies 8 of which occurred in the 90mg group (1.3%) compared to 4 in the 45mg group (0.7%). All of the malignancies reported as serious adverse events were solid tumors. Prostate cancer was the only event in this system organ class for which there were multiple reports: 1 (0.2%) in the 45 mg group and 2 (0.3%) in the 90mg group. See Section 7.3.4 for additional discussion of malignancies.

There were 14 serious adverse events reported in the "Infections and infestations" SOC with 7 events reported in each dosage group (1.2% in both groups). The events for which there were multiple reports were: cellulitis [2 (0.3%) in the 45 mg group and 1 (0.2%) in the 90 mg group] and diverticulitis [1 (0.2%) in the 45 mg group and 2 (0.3%) in the 90 mg group]. There were no

reports of salmonella or mycobacterial infections. See Section 7.3.4 for additional discussion of serious infections.

In the Gastrointestinal disorders SOC, 13 serious adverse events were reported, with single reports of all events except abdominal pain for which there were 2 reports, both in the 45 mg group.

A total of 10 serious adverse events were reported in 9 subjects in the Nervous system disorders SOC, and no event was reported by more than one subject. More reports were in the 45 mg group [6 (1%): dizziness, facial palsy, facial paresis, migraine, neuralgia, sciatica and syncope. The events reported in the 90mg group were [3 (0.5%): benign intracranial hypertension, cervicobrachial syndrome and complicated migraine.

#### Serious adverse events study T12 through Week 24

From Appendix A.1, the SOC with multiple reports of serious adverse events were Gastrointestinal disorders and Infections and infestations, and there were no multiple reports of any serious adverse events in either of these SOC (i.e. single reports of each event). More events were reported in the 90mg group in both SOC. Five events occurred in the Gastrointestinal disorders SOC, one (0.5%) in the 45mg (pancreatitis) and four (1.2%) in the 90mg group. The events were gastritis, ileus, intestinal obstruction, pancreatitis, and uvulitis.

SOC. All six infectious serious adverse events were reported in the 90mg group and were reported for five subjects. The events were appendicitis, gastrointestinal infection, pneumonia, pneumonia staphylococcal, subcutaneous abscess, and urosepsis.

There were two malignancies: breast cancer (45mg) and mycosis fungoides (90mg).

### 7.3.3 Dropouts and/or Discontinuations

Discontinuations are discussed below.

#### Discontinuations in T09 through Week 100

Per Appendix 4, the most common reasons for discontinuation were in the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC (24 subjects; 2.0%): 8 (1.3%) in the 45 mg group and 16 (2.6%) in the 90 mg group. Basal cell carcinoma was the most frequently reported malignancy for which study agent was discontinued: 5 (0.8%) in the 45 mg group and 4 (0.7%) in the 90 mg group. Prostate cancer was the second most common malignancy for which subjects were discontinued: one subject (0.2%) in the 45mg group and two subjects (0.3%) in the 90 mg group. (It should be noted that the protocol required discontinuation for malignancy.) "Pregnancy, puerperium and perinatal conditions" was the SOC with the second highest proportion of discontinuations [7 subjects (0.6%)]. "Cardiac disorders" was the reason for discontinuation for five subjects (0.4%), and myocardial infarction was the only event for which there was more than one report: 1 subject (0.2%) in each dosage group. A total of 3 subjects discontinued for infections: 2 (0.3%) in the 45 mg group and 1 (.2%) in the 90 mg group. The events were osteomyelitis, pneumonia and wound infection. One subject (0.2%) discontinued for a nervous system disorder, and the event was "headache."

#### Discontinuations in T12 through Week 24

Per Appendix A.2, 11 subjects randomized to ustekinumab discontinued study agent due to an adverse event and the proportions were similar between the dosage groups: 4 (1.9%) in the 45 mg group and 7 (2.0%) in the 90 mg group. Of the 11, 3 had discontinued since the 120-day Safety Update, and all were in the 90 mg group. Basal cell carcinoma was the only event for which there were multiple reports: 1 (0.5%) in the 45mg group and 2 (0.6%) in the 90mg group. There were single event reports for all other reasons for discontinuation. There were 2 subjects (both in the 90 mg group) who discontinued study for infections, and 3 events were reported: gastrointestinal infection, pneumonia staphylococcal and urosepsis. One subject discontinued due to myocardial infarction. No subjects discontinued due to a nervous system disorder.

### 7.3.4 Significant Adverse Events

Other significant events are discussed below.

#### **Serious Infections**

In T09, 6 additional serious infections were reported after Week 52 through Week 100: 2 reports of cellulitis (both in 45mg group), and one report each of perianal abscess (45mg), streptococcal throat infection (90mg), urinary tract infection (90mg), and pneumonia (90mg). All of the subjects recovered. None of the subjects discontinued treatment. There was no correlation with dosage group.

In T12, 3 additional subjects reported serious infections after Week 12 through Week 24. Two of these events occurred in ustekinumab-treated subjects (both in the 90mg group): back abscess and pneumonia and one in an etanercept-treated subject: cellulitis.

#### **Malignancies**

##### T09

In T09, 14 subjects reported a total of 14 malignancies between Weeks 52 and 100. Of the 14 malignancies, 3 were nonmelanoma skin cancers (all basal cell carcinomas), and 11 were solid tumors. Additional information is presented about the solid tumors:

- Subject 404-025 (45mg): a 35-year-old male reported a melanoma in situ of the lower left abdomen on Day 525.
- Subject 015-032 (45mg): a 50-year-old male reported prostate cancer on Day 523.
- Subject 130-023 (45mg): a 48-year-old male reported 4 transitional cell carcinomas in bladder on Day 613.
- Subject 404-019 (45mg): a 62-year-old male reported an adenocarcinoma of the head of pancreas on Day 487.
- Subject 300-006 (90 mg): a 57-year-old male reported adenocarcinoma of the prostate on Day 591.
- Subject 019-042 (90mg): a 66-year-old male reported metastatic kidney cancer on Day 556 leading to death. The applicant reported this death in the 120-day Safety Update (see Medical Officer's review of the original submission.)

- Subject 011-014 (90mg): a 65-year-old male reported colon cancer (well-differentiated adenocarcinoma of the rectum) on Day 681 on routine screening colonoscopy. He was treated with low anterior resection. He had 2 positive lymph nodes and no distal metastases.
- Subject 014-017 (90mg): a 53-year-old male reported melanoma in situ (behind right ear) on Day 393.
- Subject 010-001 (90mg): a 57-year-old male reported prostate cancer on Day 497.
- Subject 118-010 (90mg): a 54-year-old menopausal woman reported endometrial carcinoma (noninvasive adenocarcinoma) on Day 474. She developed intermittent vaginal bleeding which led to an ultrasound showing endometrial thickening.
- Subject 131-011 (90mg): a 64-year-old female reported breast cancer (mixed invasive ductal and lobular carcinoma, moderately differentiated) on Day 493.

In total, through Week 100, 30 malignancies have been reported in 26 ustekinumab-treated subjects. A total of 12 solid tumors were reported in 12 ustekinumab-treated subjects:

- 3 cases of prostate cancer,
- 2 each urinary cancers and melanoma in-situ, and
- 1 each breast, colon, pancreatic, squamous cell tongue, and endometrial cancer)

A hepatic neoplasm was reported in a placebo-treated subject during the first 12 weeks of the study. There was no apparent pattern to the types of malignancies that occurred in ustekinumab-treated subjects.

## T12

In T12, 3 additional subjects reported malignancies cancers after Week 12 through Week 24. There were two reports of nonmelanoma skin cancers (both basal cell carcinomas), one each in an etanercept subject and a 90 mg ustekinumab subject. The third malignancy was a cutaneous T-cell lymphoma. This subject was a 65-year-old male who had received two doses of 90 mg usttekinumab (Days 1 and 2). He was noted to have an ulcer on his finger at Week 6, and a biopsy of the lesion was reported as “atypical lymphohistiocystic infiltrate.” The ulceration was at a site where there had previously been a psoriatic plaque (or what was thought to have been one). Biopsies were taken from multiple sites on Day 125 (September 10, 2007), and “mycosis fungoides” was diagnosed. On February 29, 2008, biopsies were taken from plaques that were clinically-typical of psoriasis, and the specimens were reported as “mycosis fungoides.” The reviewer agrees with the investigator that this subject likely had the malignancy at enrollment (rather than psoriasis). The reviewer thinks it improbable that the malignancy was related to the two doses of study product.

## Cardiovascular Events

In T12, one serious cardiovascular serious adverse event was reported after Week 12 through Week 24, and it was reported in the etanercept group (supraventricular tachycardia). No strokes were reported.

In T09, the proportion of subjects reporting cardiac disorder adverse events including serious events was similar between the 45mg and 90mg dose groups: 17 (2.8%) and 16 (2.6%),

respectively for all cardiac events and 8 (1.3%) and 8 (1.3%) for serious events. After Week 52 through Week 100, 10 serious cardiovascular events were reported in 7 subjects:

- Subject 008-009 (90mg): A 71-year-old female reported atrial fibrillation on Day 409. Cardiac enzymes remained normal and a follow-up stress test did not reveal any cardiac ischemia. She remained in the study.
- Subject 016-005 (45mg): A 57-year-old male reported acute myocardial infarction on Day 688. Past medical history included dyslipidemia and smoking (> 60 pack year). He had successful stenting of his left anterior descending (LAD) artery. He remains in the study.
- Subject 016-054 (90mg): 51-year-old female reported unstable angina on Day 545. She had 2 hospitalizations approximately a week apart. Past medical history included hypertension, hyperlipidemia, and a family history of “premature” arteriosclerotic cardiovascular disease. Angiogram revealed 2-vessel disease. She underwent percutaneous coronary intervention (PCI). The stent restenosed in one of her coronary arteries approximately 4 months later. The procedure was successfully repeated. She remained in the study and has not had any recurrent cardiac events.
- Subject 019-012 (90mg): a 60-year-old male reported unstable angina on Day 679. Past medical history included, diabetes, hypertension, hyperlipidemia, and a family history of premature arteriosclerotic cardiovascular disease. Cardiac enzymes were normal. Angiogram revealed multivessel disease. He underwent successful coronary artery bypass grafting. He remained in the study.
- Subject 100-013 (90mg): a 67-year-old male reported myocardial infarction on Day 600. Past medical history included arteriosclerotic cardiovascular disease, diabetes, hypertension, hypercholesterolemia requiring medical therapy, and history of tobacco use. He underwent 3-vessel CABG. He was discontinued from the study.
- Subject 108-004 (45mg): a 55-year-old male reported 3 ischemic cardiac events: unstable angina on Days 533 and 615 and acute coronary syndrome (ACS) on Day 655. Past medical history including arteriosclerotic cardiovascular disease treated with CABG, diabetes, hypertension, and hyperlipidemia. He had multiple admissions for ischemic chest pain, twice treated with coronary stenting. He had prophylactic placement of automatic implantable cardiovascular defibrillator. He was discontinued from the study.
- Subject 411-011 (45mg): a 52-year-old male reported 2 events: myocardial infarction and CAD on Day 499 and Day 505, respectively. Past medical history included diabetes, hypertension, dyslipidemia, obesity and tobacco use. He developed chest pain, and cardiac enzymes were consistent with MI. He underwent stenting of one vessel. He remained in the study and has not had recurrent cardiac events.

There was no apparent pattern to the types of serious cardiovascular events that occurred in ustekinumab-treated subjects.

### **Neurologic Event**

An additional significant neurologic events is described below (the other was the HIV + subjective with progressive neurologic deterioration):

Subject C0743T09-006-017 (ustekinumab 45 mg group): reversible posterior leukoencephalopathy syndrome

This subject was a 65-year-old female with a history of hypercholesterolemia, alcohol abuse and smoking. She received 11 doses of ustekinumab through September 11, 2008. Apparently, on \_\_\_\_\_, her husband found her unconscious. She had regained consciousness by the time an ambulance arrived, but was confused. She presented to the emergency room (ER) with nausea, vomiting, headache and seizure activity. The seizure activity was primarily focal of the eyes. She had a witnessed seizure in the ER and received lorazepam. She did not recover to a normal state of consciousness. Her eyes were deviated toward the left, and she had "flexing" of her left arm. Her other limbs were stiff and trembled slightly. She had right focal facial paresis and "slightly less vigorous" movement on the right side. Her blood pressure was 152/92 mm Hg. She had another witnessed seizure following which her eyes were deviated to the left for about one minute in a postictal state. Bilateral Babinski signs were present. She was admitted to the intensive care unit (ICU) where she was intubated. She had a fever of 39.3°C and she was started on piperacillin and acyclovir empirically.

b(6)

Computed tomography (CT) scans showed left hypothalamic hypodensity and white matter changes in the cerebellar region and no evidence of mass effect, bleeding, or thrombosis. A magnetic resonance imaging (MRI) scan showed hyperintense anomalies in the cerebral hemispheres and upper portion of the left thalamus and in the right and possibly left parietal periventricular white matter. The pattern suggested reversible posterior leukoencephalopathy syndrome (RPLS). CT angiogram results were normal. Preliminary results of an electroencephalogram (EEG) showed absence of epileptic activity. Lumbar puncture showed no white blood cells (WBC), 9 red blood cells (RBC), slightly elevated total protein and a normal glucose. Polymerase chain reaction (PCR) testing for herpes simplex virus (HSV), West Nile virus was negative, and testing for Jakob-Creutzfeldt (JC) was negative.

She improved and was extubated within 24 hours. She remained confused for several days and inconsistently followed commands. No new seizure activity was noted, and she received only supportive care. The neurologist considered the following diagnostic possibilities: alcohol withdrawal, ischemic stroke, sepsis, encephalitis, paraneoplastic limbic encephalitis, PML, and reversible posterior leukoencephalopathy syndrome (RPLS).

She was discharged on \_\_\_\_\_ with a final diagnosis of RPLS secondary to ustekinumab. She made a full neurologic recovery. The investigator assessed the event as severe in intensity and possibly related to treatment with study agent.

b(6)

Reversible posterior leukoencephalopathy syndrome has been reported with bevacizumab (Avastin), another recombinant humanized monoclonal IgG1 antibody (Glusker et al., N Engl Med 2006; 354:9; 980-981 and Ozcan et al.; N Engl Med 2006; 354:9; 981). However, bevacizumab has a different mechanism of action than that of ustekinumab. Per the package insert, bevacizumab binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. It is indicated for treatment of a variety of malignancies.

### 7.3.5 Submission Specific Primary Safety Concerns

See the Medical Officer's review of the original submission.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Common adverse events are discussed below.

#### T09

The overall frequency of adverse events was similar between treatment groups through Week 100. Specific types of adverse events that occurred with a frequency of  $\geq 5\%$  generally occurred with a similar frequency between treatment groups. As was the case through 12 weeks of treatment, the system organ class in which adverse events were most frequently reported through Week 100 was Infections and infestations, and events were reported in 73.3% of subjects in the 45mg group and 71.9% in the 90mg group. The two most frequently reported adverse events in both treatment groups were nasopharyngitis and upper respiratory infection. While there were no reports of salmonellosis, unspecified gastroenteritis was reported in 5.8% in the 45mg group and 5.1% in the 90mg group. There were no reports of atypical mycobacterial infections. Four events occurred with a difference of  $> 1\%$  between treatment groups: upper respiratory infection: 23.6% in 45mg group, 20.3% in 90mg group; bronchitis: 7.3% in 45mg and 5.6% in 90mg; sinusitis: 5.6% in 45 mg and 7.1% in 90mg; pharyngolaryngeal pain: 3.3% in 45mg and 5.0% in 90mg. The second most common system organ class in which adverse events were reported was Musculoskeletal and connective tissue disorders: 30.0 % in the 45mg group and 30.2% in the 90mg group. No dose relationship was appreciated for common adverse events.

**Attachment 4.5 Number of subjects with 1 or more treatment-emergent adverse events (with frequency of 5% or greater) through Week 100 by MedDRA preferred term; treated subjects**

	Ustekinumab		
	45 mg <sup>a,b</sup>	90 mg <sup>a</sup>	Combined
Subjects treated	606	606	1212
Avg duration of follow-up (weeks)	87.58	88.99	88.28
Avg exposure (weeks)	77.37	78.11	77.74
Subjects with 1 or more adverse events	548 (90.4%)	548 (90.4%)	1096 (90.4%)
<b>Preferred terms</b>			
Nasopharyngitis	177 (29.2%)	184 (30.4%)	361 (29.8%)
Upper respiratory tract infection	143 (23.6%)	123 (20.3%)	266 (21.9%)
Headache	61 (10.1%)	58 (9.6%)	119 (9.8%)
Influenza	52 (8.6%)	50 (8.3%)	102 (8.4%)
Back pain	52 (8.6%)	47 (7.8%)	99 (8.2%)
Arthralgia	47 (7.8%)	50 (8.3%)	97 (8.0%)
Hypertension	47 (7.8%)	45 (7.4%)	92 (7.6%)
Bronchitis	44 (7.3%)	34 (5.6%)	78 (6.4%)
Sinusitis	34 (5.6%)	43 (7.1%)	77 (6.4%)
Cough	34 (5.6%)	35 (5.8%)	69 (5.7%)
Gastroenteritis	35 (5.8%)	31 (5.1%)	66 (5.4%)
Diarrhoea	34 (5.6%)	30 (5.0%)	64 (5.3%)
Pharyngolaryngeal pain	20 (3.3%)	30 (5.0%)	50 (4.1%)

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

<sup>b</sup> Subjects randomized to 45 mg who had a dose escalation to 90 q8 wks are included in the 45 mg group.

T12

Through Week 24, 209 subjects in the 45mg group and 347 subjects in the 90mg group received ustekinumab and were evaluated for safety, and the proportion of subjects experiencing at least one adverse event was somewhat higher in the 90mg group: 76.6% and 81.6%, respectively.

As with T09, the SOC in which adverse events were most frequently reported through Week 24 was Infections and infestations, and events were reported in 51.2% of subjects in the 45 mg group and 47.0% in the 90 mg group. The two most frequently reported adverse events in both

treatment groups were nasopharyngitis (19.6% in the 45mg group and 19.3% in the 90mg group) and headache (14.8% in the 45mg group and 13.5% in the 90mg group). Upper respiratory infection was the second most frequently reported event in the Infections and infestations SOC in both treatment groups (2.9% in the 45mg group and 12.7% in the 90mg group).

Through Week 24, 347 subjects were treated with etanercept, and 197 of these subjects crossed over to treatment with ustekinumab 90mg (etanercept → 90mg). These subjects received an average 23.2 doses of etanercept prior to crossover and 1.6 doses of ustekinumab post crossover. The average duration of follow-up was 19.9 and 6.7 weeks, pre and post crossover, respectively. Nasopharyngitis and upper respiratory tract infection were the most common adverse events pre and post crossover.

#### 7.4.2 Laboratory Findings

Markedly abnormal laboratory values are defined in the following table (for 24-week statistical analysis plan of study T12):

<b>Table 4 Markedly Abnormal Criteria for Laboratory Values</b>	
<b>Hematology Test</b>	<b>Criteria for Markedly Abnormal Status</b>
Hemoglobin (g/dL)	Decrease > 2 AND Value < 10.0
Hematocrit (%)	Value < 27
Platelets (x10 <sup>3</sup> /μL)	Percent decrease ≥ 50 AND Value < 75
WBC (x10 <sup>3</sup> /μL)	Value < 2.0 OR Value > 20.0
Eosinophils, absolute (x10 <sup>3</sup> /μL)	Percent increase ≥ 100 AND Value > 0.8
Lymphocytes, absolute (x10 <sup>3</sup> /μL)	Percent decrease ≥ 33 AND Value < 1.0
Neutrophils, absolute (x10 <sup>3</sup> /μL)	Percent decrease ≥ 33 AND Value < 1.5
<b>Chemistry Test</b>	<b>Criteria for Markedly Abnormal Status</b>
BUN/Urea (mg/dL)	Percent increase ≥ 66 AND Value > 40
Creatinine (mg/dL)	Percent increase ≥ 66 AND Value > 1.5
Total bilirubin (mg/dL)	Percent increase ≥ 100 AND Value > 3.0
Alkaline phosphatase (IU/L)	Percent increase ≥ 100 AND Value > 250
ALT (IU/L)	Percent increase ≥ 100 AND Value > 150
AST (IU/L)	Percent increase ≥ 100 AND Value > 150
Sodium (mEq/L)	(Increase ≥ 10 AND Value > 150) OR (Decrease ≥ 10 AND Value < 120)
Potassium (mEq/L)	(Increase ≥ 0.8 AND Value > 6.0) OR (Decrease ≥ 0.8 AND Value < 3.0)
Chloride (mEq/L)	Value < 85 OR Value > 120
Calcium (mg/dL)	(Increase ≥ 2.0 AND Value > 11.5) OR (Decrease ≥ 1.5 AND Value < 7.5)
Albumin (g/dL)	Decrease ≥ 1.0 AND Value < 3.0
Total protein (g/dL)	Value < 4.5 OR Value > 10.0
<b>Note: Increases and decreases above are relative to the baseline value.</b>	

#### T09

Hematology and chemistry testing is being done at each study visit in the long-term extension phase. Decreased neutrophils (1.5% in 45mg; 2.1% in 90mg), decreased lymphocytes (7.3% in 45mg; 5.0% in 90mg), and elevated eosinophils (2.2% in 45mg; 2.8% in 90mg) were the only markedly abnormal hematology values occurring in more than 1% of subjects. For each of these events, most subjects had only one report of markedly abnormal hematology value (per Attachment 4.46 of the study report). No subjects discontinued study agent due to these events.

Markedly abnormal ALT (2.3% in both dosage groups), AST (1.0% in 45mg; 2.0% in 90mg), non-fasting glucose (elevated: 16.4% in 45mg; 19.6% in 90mg; decreased: (2.7% in 45mg; 2.0% in 90mg), and creatinine (1.5% in 45mg; 0.7% in 90mg) were observed in more than 1% of subjects (Attachment 4.63).

#### T12

Hematology and chemistry testing was done at screening, Week 0 and monthly thereafter.

Decrease in absolute lymphocytes was the only markedly abnormal change to occur in more than one subject on more than one occasion in the ustekinumab groups through Week 24, occurring in 2 (0.6%) subjects in the 90mg group. There was no obvious pattern of changes over time.

Elevated ALT was the only markedly abnormal change to occur in more than one subject on more than one occasion in the ustekinumab groups through Week 24, occurring in 1 (0.5%) subject in the 45mg group and 3 (0.9%) subjects in the 90mg group 2 (0.6%) subjects in the 90mg group. There was no obvious pattern of changes over time.

#### 7.4.3 Vital Signs

In T09, vital signs are collected at each study visit. Per the Medical Officer's review of the original submission, vital signs are measured for safety purposes, and no formal analyses are being done on these data. In T12, vital signs were measured through Week 20 and next at Week 64 (end of study).

#### 7.4.4 Electrocardiograms (ECGs)

See the Medical Officer's review of the original submission.

#### 7.4.5 Special Safety Studies

No special safety studies were done.

#### 7.4.6 Immunogenicity

In T09, there were no reports of possible anaphylactic reactions or possible serum sickness-like reactions associated with study agent through Week 100. For subjects who had positive antibodies to ustekinumab, 1.6% ustekinumab injections were associated with injection-site reactions versus 0.9% for subjects who were negative for antibodies. All injection site reactions in the antibody-positive subjects were mild. From Attachment 4.66 of the study report:

**Attachment 4.66 Summary of injection-site reactions, possible anaphylactic reactions, or possible serum sickness-like reactions through Week 100 by antibody to ustekinumab status through Week 88; subjects treated with ustekinumab**

	Ustekinumab		
	45 mg <sup>a</sup>	90 mg <sup>a</sup>	Combined
Subjects treated	606	606	1212
Subjects with appropriate samples <sup>b</sup>	600	602	1202
Subjects positive for antibodies to ustekinumab at any time <sup>c</sup>	39	25	64
Subjects negative for antibodies to ustekinumab after last treatment <sup>f</sup>	561	577	1138

aPlacebo crossover subjects are included after crossover to ustekinumab.

b Subjects with appropriate samples had 1 or more samples obtained after their first study agent administration.

c Includes all subjects who had at least 1 positive sample at any time.

f Includes all subjects whose last sample was negative, and excludes subjects who were positive at any time.

In T12, 13 subjects (2.4%) tested positive for antibodies to ustekinumab through Week 24, only one of whom developed an injection site reaction. There was no correlation between dosage group and antibody positivity (7 subjects were in the 45mg group; 6 were in the 90 mg group).

The presence of the product in the serum interferes with the detection of antibodies. Therefore, at best, only tentative conclusions can be drawn about the immunogenicity potential of the product. However, the database does not reveal a signal suggesting high potential for immunogenicity.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

See Section 7.3

### 7.5.2 Time Dependency for Adverse Events

See Section 7.3.

### 7.5.3 Drug-Demographic Interactions

See the Medical Officer's review of the original submission.

### 7.5.4 Drug-Disease Interactions

See Medical Officer's review of the original submission.

### 7.5.5 Drug-Drug Interactions

See the Medical Officer's review of the original submission.

## 7.6 Additional Safety Explorations

### 7.6.1 Human Carcinogenicity

See the Medical Officer's review of the original submission.

### 7.6.2 Human Reproduction and Pregnancy Data

In T09, six additional pregnancies were reported from Week 52 through Week 100. One pregnancy was ongoing at the time of the study report, one subject was lost to follow-up. Two subjects delivered healthy females. One subject who had a history of type 2 diabetes had a spontaneous abortion. A partner of a study subject delivered a healthy female.

Three additional pregnancies were reported in T12 between Weeks 12 and 24, two of which were partner pregnancies. The pregnancies were entered into the database after the 24-week database lock.

### 7.6.3 Pediatrics and Effect on Growth

See Medical Officer's review of the original submission.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

See the Medical Officer's review of the original submission.

## 7.7 Additional Submissions

### **Subjects who received ustekinumab with particulate levels $\geq$ C**

In response to an Agency request, the applicant submitted safety and efficacy analyses for subjects who received ustekinumab with particulate levels  $\geq$  C (see Section 4.1). This submission constituted a major amendment (submit date: May 1, 2009). The applicant provided those data for trial T09. Some subjects in T08 also received drug product with particulate levels  $\geq$  C; however, the applicant does not expect to complete analyses from this trial until the third/fourth quarter of 2009 (data then available from the Week 152 database lock).

All ustekinumab administered in T09 prior to Week 52 had particulate levels  $<$  C. After this timepoint, two lots of product (one 45mg and one 90mg) had particulate levels  $\geq$  C: lot 6DS4Z (45mg) ranged from category "B" to category "D" and lot 6DS50 (90mg) ranged from category "C" to "D." Product from these lots was administered to some study subjects between Weeks 52 and 80:

- 411 subjects received at least 1 administration from Lot 6DS4Z (45 mg)
- 379 subjects received at least 1 administration from Lot 6DS50 (90 mg).

Most subjects were treated every 12 weeks according to the maintenance dosing schedule proposed in labeling and received drug product at Weeks 52, 64, and 76. Subjects who had maintenance dosing adjusted to every 8 weeks at Week 28 or 40 (as allowed by the protocol) would have received drug product at other Weeks 60 and 56, respectively.

The applicant analyzed efficacy and adverse events in subjects who were PASI 75 responders at Week 28 and at Week 40 and remained on a maintenance dosing schedule of every 12 weeks at Week 64, choosing this subpopulation because:

- It is the largest subpopulation with a total of 394 subjects (195 subjects in the 45 mg group and 199 subjects in the 90 mg group);
- Subjects were on a uniform dosing schedule.

After the Week 52 database lock, T09 was unblinded, and all drug was supplied in prefilled syringes (PFS). Unblinding occurred between Week 60 and Week 84 (depending on the subject's randomization date). Therefore, data using the liquid-in-vial (LIV) presentation are available for the visit prior to unblinding on each subject (weeks 56-80), depending on their initial date of randomization. The proportion of subjects receiving drug product with the LIV progressively decreased through Week 80. The applicant generally excluded data from subjects dosed with PFS to avoid any confounding in the analyses.

The remainder of this page is intentionally left blank.

**Applicant's Table 1 Number of subjects treated with ustekinumab in LIV beyond Week 52 who received ustekinumab from lots with visible particulates < C versus ≥ C; subjects randomized at Week 0 who continued study agent at Week 52 or beyond**

	Ustekinumab <sup>a</sup>		
	45 mg	90 mg	Combined
<b>Week 52</b>			
n	492	509	1001
Visible particulate level < C	466 (94.7%)	493 (96.9%)	959 (95.8%)
Visible particulate level ≥ C	26 (5.3%)	16 (3.1%)	42 (4.2%)
<b>Week 56</b>			
n	40	32	72
Visible particulate level < C	28 (70.0%)	26 (81.3%)	54 (75.0%)
Visible particulate level ≥ C	12 (30.0%)	6 (18.8%)	18 (25.0%)
<b>Week 60</b>			
n	76	59	135
Visible particulate level < C	50 (65.8%)	39 (66.1%)	89 (65.9%)
Visible particulate level ≥ C	26 (34.2%)	20 (33.9%)	46 (34.1%)
<b>Week 64</b>			
n	364	390	754
Visible particulate level < C	153 (42.0%)	179 (45.9%)	332 (44.0%)
Visible particulate level ≥ C	211 (58.0%)	211 (54.1%)	422 (56.0%)
<b>Week 68</b>			
n	54	36	90
Visible particulate level < C	7 (13.0%)	13 (36.1%)	20 (22.2%)
Visible particulate level ≥ C	47 (87.0%)	23 (63.9%)	70 (77.8%)
<b>Week 72</b>			
n	13	12	25
Visible particulate level < C	1 (7.7%)	1 (8.3%)	2 (8.0%)
Visible particulate level ≥ C	12 (92.3%)	11 (91.7%)	23 (92.0%)
<b>Week 76</b>			
n	91	96	187
Visible particulate level < C	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visible particulate level ≥ C	91 (100.0%)	96 (100.0%)	187 (100.0%)
<b>Week 80</b>			
n	2	1	3
Visible particulate level < C	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visible particulate level ≥ C	2 (100.0%)	1 (100.0%)	3 (100.0%)

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

From the above table, there was great variation in the number of subjects who received this product from one treatment visit to the next; however, the proportion of subjects who received these products progressively increased for each treatment visit. The highest number in both treatment groups was at Week 64. All subjects in both treatment groups received product with particulate levels  $\geq C$  at Weeks 76 and 80; however the numbers of subjects were substantially lower at Week 80 compared to Week 76.

Efficacy

**From Applicant’s Table 2 Summary of PASI response at Week 64 and Week 76 by visible particulate level in LIV ustekinumab received at Week 64; subjects randomized at Week 0 who were PASI 75 responders at Week 28 and at Week 40 and continued q12 week dosing at Week 64**

	Visible Particulate Level < C at Week 64 <sup>a</sup>		Visible Particulate Level $\geq C$ at Week 64	
	45mg	90mg	45mg	90mg
Week 64	n=139 119 (85.6%)	n= 167 142 (85.0%)	n= 195 164 (84.1%)	n= 198 170 (85.9%)
Week 76	n=136 111 (81.6%)	n=162 136 (84.0%)	n=193 159 (82.4%)	n=196 166 (84.7%)

<sup>a</sup>Excludes subjects who received ustekinumab with visible particulate level  $\geq C$  at Week 52.

PASI responses were similar between the particulate groups for the subjects included in these analyses at the timepoints evaluated. Administration of product with visible particulate level  $\geq C$  does not appear to have negatively impacted efficacy.

Adverse Events

The safety issue pertaining to use of the OOT product, is whether the product increased immunogenicity. The proportions of subjects who experienced one or more treatment-emergent adverse events were generally similar when subjects who received ustekinumab with particulates  $\geq C$  were compared to subjects who received product with levels < C. For both treatment groups (45mg and 90mg), the proportions of treatment-emergent adverse events were slightly higher in subjects who received particulates with levels  $\geq C$  compared to those who received with particulates < C. Overall, the proportions of treatment-emergent adverse events were highest in subjects who received 90mg doses of product with particulates  $\geq C$  and lowest for those who received 45mg doses with levels < C. Per Attachment 1, nasopharyngitis and upper respiratory tract infections were the two most common adverse events in both treatment groups irrespective of particulate level, i.e. < C or  $\geq C$ . There were no reports of anaphylaxis or serum sickness-like reactions. Per Attachment 1, there was one report in the “Immune system disorders” SOC: Drug hypersensitivity in a subject who received 90mg with particulates  $\geq C$ . However, this event was not reported as a serious adverse event.

A total of eight serious adverse events occurred in subjects who received doses of product with particulates  $\geq C$ , and none of the events appeared to be immune-mediated. The numbers of subjects who experienced serious adverse events was highest for subjects who received 45mg

doses of product with particulates  $\geq$  C. The specific events and the dosage group in which they occurred follow:

45mg Group

- Wrist fracture
- Adenocarcinoma of the pancreas
- Gastric
- Non-cardiac chest pain
- Myocardial infarction and coronary artery disease

90 mg Group

- Carbon monoxide poisoning
- Rib fracture and pneumothorax
- Chest pain

The remainder of this page is intentionally left blank.

**Applicant's Table 4: Number of subjects with 1 or more treatment-emergent adverse events, serious adverse events, infections, and adverse events leading to discontinuation from Week 64 through Week 76 by visible particulate level in LIV ustekinumab received at Week 64; treated subjects who were PASI 75 responders at Week 28 and at Week 40 and continued q12 weeks dosing at Week 64**

	Ustekinumab <sup>a</sup>					
	Visible Particulate Level < C at Week 64 <sup>b</sup>			Visible Particulate Level ≥ C at Week 64		
	45 mg	90 mg	Combined	45 mg	90 mg	Combined
Treated subjects who were PASI 75 responders at Week 28 and at Week 40 and continued q12 weeks dosing at Week 64	139	167	306	195	199	394
Avg duration of follow-up (weeks)	12.3	12.1	12.2	11.9	11.9	11.9
Subjects with 1 or more adverse events	39 (28.1%)	63 (37.7%)	102 (33.3%)	65 (33.3%)	80 (40.2%)	145 (36.8%)
Subjects with 1 or more serious adverse events	0 (0.0%)	2 (1.2%)	2 (0.7%)	5 (2.6%)	3 (1.5%)	8 (2.0%)
Subjects with 1 or more infections	19 (13.7%)	33 (19.8%)	52 (17.0%)	37 (19.0%)	35 (17.6%)	72 (18.3%)
Subjects with 1 or more adverse events leading to discontinuation	1 (0.7%)	2 (1.2%)	3 (1.0%)	1 (0.5%)	0 (0.0%)	1 (0.3%)

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

<sup>b</sup> Excludes subjects who received ustekinumab with visible particulate level ≥ C at Week 52.

### Immunogenicity

The applicant reported that no new subjects developed antibodies to ustekinumab after Week 52 and through Week 88. This is inclusive of the 790 subjects who were exposed to ustekinumab with particulate levels ≥ C. The 64 subjects who had antibodies to ustekinumab at Week 88 were antibody-positive prior to receiving any product with particulate levels ≥ C.

**Applicant's Attachment 2 Summary of antibody to ustekinumab status through Week 52; treated subjects**

	Ustekinumab				
	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg	Combined
Subjects treated	197	195	409	411	1212
Subjects with appropriate samples <sup>a</sup>	195	195	405	407	1202
Subjects positive for antibodies to ustekinumab at any time <sup>b,c</sup>	16 (8.2%)	4 (2.1%)	24 (5.9%)	21 (5.2%)	65 (5.4%)
Subjects negative for antibodies to ustekinumab after last treatment <sup>b,d</sup>	36 (18.5%)	23 (11.8%)	84 (20.7%)	50 (12.3%)	193 (16.1%)
Subjects with undetectable antibody to ustekinumab status after last treatment <sup>b,e</sup>	143 (73.3%)	168 (86.2%)	297 (73.3%)	336 (82.6%)	944 (78.5%)

- <sup>a</sup> Subjects with appropriate samples had 1 or more samples obtained after their first study agent administration.
- <sup>b</sup> Denominator is subjects with appropriate samples.
- <sup>c</sup> Includes all subjects who had at least 1 positive sample at any time.
- <sup>d</sup> Includes all subjects whose last sample was negative, and excludes subjects who were positive at any time.
- <sup>e</sup> Includes all subjects whose last sample could not be classified as negative due to potential interference from circulating active study agent, and excludes subjects who were positive at any time.

**Summary of serious adverse events in C0743T08**

Safety data from this trial were not provided in the Complete Response (except for deaths) as there had been no database lock since the 120-Day Safety Update in which data through Week 76 were reported. However, the applicant provided a summary of serious adverse events that occurred since the Week 76 database lock through October 31, 2008 in response to an Information Request. These data do not reflect formal analyses (database was not locked).

After the Week 76 database lock and through October 31, 2008, 28/657 (4.3 %) subjects reported serious adverse events. There were seven reports of serious infections (1.1%): pancreatitis (unclear why this was reported as an infectious event), pneumonia, osteomyelitis, infectious diarrhea (not further specified), pyelonephritis, bronchitis, and "intestinal perforation."

There were four reports of solid tumor malignancies (0.6%): three reports of prostate cancer (all subjects had elevated prostate specific antigen at baseline on retrospective testing) and lymphoma. However, the lymphoma was not documented (i.e. it was "suspected"): lymph node and bone marrow biopsies did not reveal lymphoma.

The summary data raised no new safety concerns.

**Applicant's Appendix 1: Number of subjects with 1 or more serious treatment-emergent adverse events since the Week 76 database lock by MedDRA preferred term; subjects still in the study as of the Week 76 database lock**

Subjects still in the study as of the Week 76 database lock	657
Subjects with 1 or more serious adverse events <sup>a</sup>	28 (4.3%)
Preferred terms	
Prostate cancer	3 (0.5%)
Abortion spontaneous	2 (0.3%)
Coronary artery disease	2 (0.3%)
Drug eruption	2 (0.3%)
Myocardial infarction	2 (0.3%)
Atrial fibrillation	1 (0.2%)
Atrial flutter	1 (0.2%)
Benign prostatic hyperplasia	1 (0.2%)
Bradycardia	1 (0.2%)
Bronchitis	1 (0.2%)
Chronic hepatic failure	1 (0.2%)
Colitis	1 (0.2%)
Deafness neurosensory	1 (0.2%)

Diarrhoea infectious	1 (0.2%)
Drug dependence	1 (0.2%)
Endometrial hyperplasia	1 (0.2%)
Fall	1 (0.2%)
Femur fracture	1 (0.2%)
Gastritis	1 (0.2%)
Intestinal perforation	1 (0.2%)
Lymphoma	1 (0.2%)
Nephrolithiasis	1 (0.2%)
Open fracture	1 (0.2%)
Osteoarthritis	1 (0.2%)
Osteomyelitis	1 (0.2%)
Pneumonia	1 (0.2%)
Polydactyly	1 (0.2%)
Presyncope	1 (0.2%)
Pyelonephritis	1 (0.2%)
Renal failure	1 (0.2%)

## 8 Postmarketing Experience

Postmarketing experience is underway as the product is now approved in other jurisdictions (see Section 2.6).

## 9 Appendices

### 9.1 Literature Review/References

See the Medical Officer's review of original submission and the body of this review.

### 9.2 Labeling Recommendations

Recommendations for labeling will be placed at the end of this review.

### 9.3 Advisory Committee Meeting

See the Medical Officer's review of original submission.

22 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

---

MEMORANDUM

---

DATE: December 18, 2008

TO: File, BLA 125261 STELARA (ustekinumab)  
Centocor, Inc

FROM: Julie Beitz, M.D.  
Director, Office of Drug Evaluation III

RE: Complete Response Action

---

Ustekinumab is a fully human IgG1 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 differentiation and activation of T helper (Th)1 and Th17 cells, thereby inhibiting immune pathways important to the pathogenesis of psoriasis. This memo documents my concurrence with the Division of Dermatology and Dental Product's (DDDP's) complete response action for ustekinumab, administered by subcutaneous (SC) injection, for use in adult patients with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

BLA 125261, dated November 28, 2007, was received on November 29, 2007 and granted a standard review. The application was discussed before the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) on June 17, 2008. Several issues were addressed including, efficacy considerations related to weight-based dosing, safety considerations (e.g., risks associated with prolonged immunosuppression), and the utility of various strategies to monitor short- and long-term safety in exposed patients (e.g., prescriber administration vs. self-administration, enrollment in a mandatory patient registry vs. a post-approval observational study).

Before this application may be approved, the sponsor must 1) address deficiencies involving chemistry, manufacturing and controls (CMC), and 2) submit a proposed Risk Evaluation and Mitigation Strategy (REMS) as described below. The CMC deficiencies and information needed for their resolution were conveyed to the sponsor in a Discipline Review letter on November 19, 2008. Product labeling remains unresolved at this time.

## CHEMISTRY, MANUFACTURING AND CONTROLS

On August 18, 2008, Centocor submitted updated drug product stability data that showed an unexpected increase in visible particulates in lots on stability at 2-8°C. Centocor's investigation suggested that the particulates were a result of \_\_\_\_\_ leaching from the \_\_\_\_\_ vials for the visible particulate assay, and was, therefore, an artifact created during the assay procedure. The Division of Monoclonal Antibodies (DMA) questioned this explanation given that the assay had undergone validation with no issue of leachables previously identified, and no differences were observed in the level of visible particulates between samples \_\_\_\_\_ glass syringes and assayed at a different site. As there is currently insufficient information to identify the root cause for the problem, and to support use of the current visible particulate test and sampling method for release and stability testing, DMA has recommended that the BLA not be approved at this time. Prior to approving ustekinumab, the sponsor will need to identify the root cause of the increase in visible particulates, outline corrective actions taken, and develop and validate a sampling and testing method for assessment of the level of visible particulates in the drug product.

b(4)

## EFFICACY

Two randomized controlled trials (PHOENIX 1 and PHOENIX 2) evaluated the efficacy of injections of ustekinumab 45 mg and 90 mg relative to placebo. A total of 766 and 1230 patients were enrolled in these trials, respectively. Patients were randomized 1:1:1 to 45 mg, 90 mg or placebo, dosed at Weeks 0 and 4, and assessed at Week 12. Patients randomized to placebo were crossed over at Week 12 to active treatment. High proportions of patients in both ustekinumab groups (66% to 76%) achieved a Psoriasis Area and Severity Index 75 (PASI 75) response at Week 12 (the primary endpoint) compared with 3-4% of placebo-treated patients. In addition, the Physician Global Assessment (PGA) of psoriasis of cleared or minimal was noted for 60-73% of ustekinumab-treated patients as compared to 4-5% for placebo-treated patients. Evidence for maintenance of effect through one year in patients receiving maintenance doses every 12 weeks was also demonstrated.

In patients weighing > 100 kg, efficacy was reduced and serum concentrations were lower in those who received 45 mg compared to 90 mg. Patients > 100 kg who received 90 mg had similar serum concentrations as patients ≤ 100 kg who received 45 mg. These observations lead the applicant to propose dosing patients ≤ 100 kg with 45 mg and patients > 100 kg with 90 mg. The Advisory Committee unanimously recommended approval of ustekinumab with a majority voting in favor of the sponsor's proposed weight-based dosing paradigm. Further discussion to optimize weight-based dosing for this product will be deferred to the next review cycle.

## PHARMACOKINETIC CONSIDERATIONS

Ustekinumab is slowly absorbed after a single SC injection and reaches maximum serum concentration in 7-14 days. The bioavailability of ustekinumab is estimated to be 57% following a single SC injection. The median half-life is approximately 3 weeks, similar to a typical half-life for an endogenous IgG. Based on population pharmacokinetic

analyses, patient weight is the most clinically relevant factor in determining optimal dosing.

## **SAFETY**

**Background.** Ustekinumab is an immunosuppressant to be used chronically in psoriasis patients. Risks of chronic immunosuppression include serious infections and malignancy. Ustekinumab cannot be tested in a traditional 2-year rodent study to evaluate carcinogenic potential; species-specific binding limits its evaluation to humans and non-human primates. Published experimental data from studies with IL-12/IL-23 knockout mice showed that they developed more aggressive UV-induced tumors earlier and more frequently than wild-type mice. The relevance of these findings to cancer development in ustekinumab-treated psoriasis patients is unknown; however, it is important to consider that such patients may have had exposure to other therapies which could increase the risk of tumor development (e.g., UVB, photodynamic therapy, or other immunosuppressants). Humans genetically deficient in IL-12/IL-23 appear to have particular susceptibilities to infections from BCG, environmental mycobacteria and non-typhoidal salmonella but no apparent excess risk for malignancy, although most of these patients have yet to reach middle age. The relevance of this experience to pharmacologic IL-12/IL-23 blockade by ustekinumab is unclear.

**Clinical Observations.** The original BLA submission contained safety data on 2266 ustekinumab-treated patients, 373 of which had at least 18 months exposure. Rates of serious adverse events were low and were similar in ustekinumab- and placebo-treated patients. There was no evidence of cumulative dosing toxicity or lymphocyte depletion.

There were no cases of active TB or serious fungal infections. The most frequently reported infection requiring antimicrobial treatment was upper respiratory tract infection, which was reported in 1.1% (placebo), 0.8% (ustekinumab 45 mg), and 0.8% (ustekinumab 90 mg) of patients.

The original BLA reported a total of 21 non-melanoma skin cancers in 14 patients, and 5 reports of solid tumors (two of prostate cancer, and one report each of breast, transitional cell kidney, and thyroid cancer). These malignancies did not reveal a pattern that was suggestive of immunosuppression or a common mechanistic link. No lymphomas were reported for which psoriasis patients are reportedly at higher risk.

The incidence of antibodies to ustekinumab in phase 3 trials was 3.7%; antibody titers were low, with the majority  $\leq 1:80$ . There was no apparent effect of antibodies on efficacy or on the occurrence of injection site reactions.

A numeric imbalance in rates of major adverse cardiovascular events was observed between ustekinumab- and placebo-treated patients in the controlled portions of phase 2 and 3 trials, resulting predominantly from an imbalance in event rates from a phase 2 trial with a 4:1 randomization. Rates of major adverse cardiovascular events were consistent with expected background rates.

**Summary.** Considering all the available data, DDDP and the DODAC expressed concerns about long-term safety risks in psoriasis patients who would receive ustekinumab chronically. The DODAC cautioned unanimously that ustekinumab-treated patients had not been followed for a sufficient length of time, and that it was important to communicate the potential for malignancy to prescribers. In addition, the DODAC voted 7-4 in favor of prescriber administration of ustekinumab, in part to allow for closer patient follow-up than would likely occur with patient self-administration. The DODAC voted unanimously that the sponsor's proposals, including a 5-year extension of PHOENIX 1 and 2, and proposed observational studies would not be sufficient to characterize the long-term safety of ustekinumab.

Following the DODAC meeting, DDDP held discussions internally and with the sponsor regarding a proposed REMS for ustekinumab, as well as post-marketing requirements and commitments, to address the risks of serious infections and malignancy.

### **RISK EVALUATION AND MITIGATION STRATEGIES (REMS)**

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
- (F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of STELARA (ustekinumab) outweigh its risks of serious infections and malignancy. These risks were identified based on data from animal models and IL-12/IL-23 genetically deficient humans that suggest a theoretical risk for malignancy and susceptibility to infections.

- A. STELARA (ustekinumab) is proposed for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. It has been estimated that 7.5 million people are reported to have psoriasis.
- B. Patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy experience decreased quality of life, with significant impairment of social and occupational functioning. The severity of

their disease, which is chronic, unsightly and uncomfortable, makes topical treatment impractical.

- C. Compared to placebo, STELARA (ustekinumab) was shown to be effective for the above proposed indication.
- D. The expected duration of therapy with STELARA (ustekinumab) is at least one year.
- E. Potential adverse events that may be related to the use of STELARA (ustekinumab) include serious infections and malignancy. Based on data from rodent models, there is a theoretical concern that blockade of IL-12/IL-23 may heighten patients' risk for malignancy. Humans genetically deficient in IL-12/IL-23 appear to have particular susceptibilities to infections from BCG, environmental mycobacteria and non-typhoidal salmonella but no apparent excess risk for malignancy, although most of these patients have yet to reach middle age. There are no apparent signals for particular infection susceptibilities or malignancy in the safety database for ustekinumab submitted in support of the BLA; however, follow-up is only through 18 months. The background incidence of these events in the population likely to use the drug is unknown.
- F. The term new molecular entity (NME) is generally not used with respect to biologics. STELARA (ustekinumab) is the first member of the class of human anti-IL-12/IL-23 monoclonal antibodies.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that STELARA (ustekinumab) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of STELARA (ustekinumab). FDA has determined that STELARA (ustekinumab) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, STELARA (ustekinumab). FDA has also determined that STELARA (ustekinumab) is a product for which patient labeling could help prevent serious adverse events.

The elements of the REMS will be a Medication Guide, a Communication Plan and a timetable for submission of assessments of the REMS.

#### **POSTMARKETING REQUIREMENTS UNDER PREA**

Pediatric study requirements were discussed at a December 10, 2008, meeting of the Pediatric Review Committee (PERC). It has been determined that pediatric study requirements will be deferred for all age groups as studies in adults have been completed and approval is expected once the deficiencies outlined above have been adequately addressed.

## **POSTMARKETING REQUIREMENTS UNDER 505(o)**

In accordance with section 505(o)(3)(A), based on the signal of serious risk of serious infection and malignancy described above, we have determined that, if this application is approved, postmarketing clinical trials will be needed to further assess this risk.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of serious risk of developing serious infection or malignancy.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this signal of serious risk. Finally, we have determined that only clinical trials will be sufficient (rather than an observation study) to assess this risk of serious infection and malignancy through collection of data on adverse events and laboratory assessments, including pharmacokinetic and immunogenicity parameters, in patients receiving long-term treatment with STELARA (ustekinumab).

Therefore, based on appropriate scientific data, FDA has determined that, if this application is approved, the sponsor will be required, pursuant to section 505(o)(3) of the FDCA, to continue the treatment of patients enrolled in the PHOENIX 1 and PHOENIX 2 trials for a total of 5 years. The specific details of these required postmarketing clinical trials will be described more fully in the approval letter for this application, if it is approved.

## **POSTMARKETING STUDY COMMITMENTS**

As this time, the DDDP is considering several sponsor-proposed post-approval risk assessment and risk management activities including:

- PSOLAR (Psoriasis Longitudinal Assessment and Registry), a prospective, 8-year observational study of clinical outcomes in adult psoriasis patients receiving systemic therapies, including ustekinumab and infliximab; 4000 psoriasis patients will be exposed to ustekinumab.
- NORDIC (The Nordic Database Initiative), a prospective, 5-year observational study of clinical outcomes in patients residing in Northern European countries; the sponsor projects that 3% of adult patients will have psoriasis and 5% of these will be eligible for ustekinumab for an exposure cohort of approximately 11,000 patients.
- Pregnancy Research Initiative, a prospective, 5-year observational study of pregnancy outcomes in women with prenatal exposure to ustekinumab, and of health status of infants exposed *in utero*.

## **TRADENAME REVIEW**

The Division of Medication Error Prevention and Analysis has found the proposed tradename STELARA to be acceptable. The likelihood of confusing STELARA (vials) with STALEVO (tablets) is expected to be minimal.

*Julie Beitz* 12-18-08

---

Julie Beitz, M.D.

Director

Office of Drug Evaluation III

## DIVISION DIRECTOR SUMMARY REVIEW

<b>Date</b>	15 December 08
<b>From</b>	Susan J. Walker, M.D.
<b>Subject</b>	Summary Review
<b>BLA #</b>	125061/000
<b>Applicant Name</b>	Centocor
<b>Date of Submission</b>	29Nov2007
<b>PDUFA Goal Date</b>	29Dec2008
<b>Proprietary Name / Established (USAN) Name</b>	Stelara/Ustekinumab (CNTO 1275)
<b>Dosage Forms / Strength</b>	Liquid in Vial/45mg/0.5mL vial and 90mg/1.0 mL vial
<b>Proposed Indication(s)</b>	1. Treatment of patients 18 years and older with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
<b>Recommended Action for NME</b>	<b>Complete Response</b>

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	<b>Names of discipline reviewers</b>
Medical Officer Review	Brenda Carr, M.D.
Statistical Review	Kathleen Fritsch, Ph.D.
Pharmacology Toxicology Review	Jiaqin Yao, Ph.D.
CMC Review/OBP Review	Laurie Graham, M.S. and Vivian Wang M.S.
Microbiology Review	Bo Chi, Ph.D.
Clinical Pharmacology Review	Abimbola Adebowale, Ph.D./Jang-Ik Lee, Pharm.D.,
Pharmacogenomics Review	Ph.D.
Pharmacometrics Review	Shashi Amur, Ph.D., and Padmaja Mummaneni, Ph.D.
	Pravin Jadhav, Ph.D.
DDMAC	Andrew Haffer, Pharm.D. and Shefali Doshi, M.D.
DSI	Sherbet Samuels, R.N., M.P.H.
CDTL Review	Jill Lindstrom, M.D.
OSE/DMEPA	Loretta Holmes, BSN, Pharm. D.
OSE/DRISK	Sharon R. Mills, BSN, R.N., CCRP
OSE/DSRCS	N/A
CBER/DVRPA	Rosemary Tiernan, M.D., M.P.H.
Other	
MHT	Leyla Sahin, M.D.
SEALD	Elektra J. Papadopoulos, M.D.
DCRP	Christine E. Garnett, Pharm.D. and Norman L. Stockbridge, M.D., Ph.D.

**Division Director Review**

**OND=Office of New Drugs**

**DDMAC=Division of Drug Marketing, Advertising and Communication**

**OSE= Office of Surveillance and Epidemiology**

**DMETS=Division of Medication Errors and Technical Support**

**DSI=Division of Scientific Investigations**

**DDRE= Division of Drug Risk Evaluation**

**DSRCS=Division of Surveillance, Research, and Communication Support**

**CDTL=Cross-Discipline Team Leader**

## 1. Introduction

Ustekinumab is a first-in-class new molecular entity proposed for the treatment of plaque psoriasis. Ustekinumab is a fully humanized IgG1 $\kappa$  monoclonal antibody that binds to the p40 subunit of interleukin (IL)-12 and IL-23. These cytokines share the IL-12 p40 subunit, and have been implicated in the pathogenesis of psoriasis. This product is not currently marketed in the U.S. or in any other countries.

This review will focus primarily upon the two significant unresolved issues for this application, which are the manufacturing issues and the post marketing safety surveillance.

## 2. Background

CNTO 1275 (Ustekinumab) is a fully human IgG1 $\kappa$  monoclonal antibody to human IL-12 p40 that binds with high affinity to human IL-12 and IL-23 and neutralizes their bioactivity preventing these cytokines from binding to their IL-12RB1 (IL-12 receptor beta-1) receptor protein expressed on the surface of immune cells. CNTO 1275 is a selective immunosuppressant classified according to the proposed Anatomical Therapeutic Chemical Classification system as an Interleukin Inhibitor.<sup>1</sup> The immunosuppression is of prolonged duration because of the product's long half-life of three weeks.

The applicant has conducted two adequate and well controlled studies in which efficacy was assessed adequately using the investigator's global assessment score and the Psoriasis Area and Severity score (PASI). The product safety assessment was primarily based upon an integrated analysis of data encompassing studies through 18 months. The safety database revealed no signals suggesting that patients treated with ustekinumab might manifest vulnerability to the spectrum of infections seen in individuals genetically deficient in IL-12 and IL-23. However, the 18 month safety database is likely insufficient to fully characterize the risk of infection and malignancy for chronic use of this product.

## 3. CMC/Device

The Division of Monoclonal Antibodies (DMA) has determined that the application is not ready for approval. The applicant has submitted drug product stability data that shows an unexpected increase in visible particles detected in drug product lots on stability at 2-8 degrees C. There have been multiple attempts to resolve this issue with the applicant. Three of the four lots produced in 2008 failed the visible particulate assay at release and the one lot that passed release (Batch 8FS3Z) demonstrated an atypical increase in visible particulates over time during storage at 2-8 degrees C. There is currently insufficient information in the BLA to identify a root cause of the out-of-trend (OOT) and out-of-specification (OOS) findings, and to support the use of the current visible particulate test and sampling method for release and stability testing of ustekinumab drug product. A Complete Response is recommended DMA, with the following deficiencies and informational needs:

---

<sup>1</sup> DVRPA review 07.14.08

**Deficiencies:**

1. Control procedures need to be established to validate the performance of manufacturing processes responsible for causing variability in the drug product. Specifically, numerous drug product lots have recently failed specification for visible particulate at release or stability. The application lacks documentation of an event that can reasonably be determined to have caused the visible particulate assay out-of-specification results.
2. The application lacks an accurate testing and sampling method for measurement of visible particulate matter that has been developed, documented, and reviewed, and approved by Centocor's Quality Control Unit.

**Information Needed:**

1. Identification of the root cause of the out-of-specification (OOS) results for the visible particulate assay supported by a comprehensive, consistent narrative of the investigation into the OOS events with data that strongly and directly support the conclusion. The root cause investigation should also outline corrective actions taken that assure consistent drug product manufacture and testing.
2. Development and validation of a robust sampling and testing method for assessment of the level of visible particulates in the drug product. Development and validation results should provide assurance that the assay is able to consistently and reproducibly perform its intended function. The assay should be reviewed and approved by Centocor's Quality Control Unit.

The Office of Biotechnology Products (Division of Monoclonal Antibodies) and Office of Compliance (Division of Manufacturing and Product Quality) concurred in waiving a pre-approval inspection at the drug product manufacturing facility (Cilag AG, Switzerland). The waiver was recommended as there are "no substantive differences between the drug product manufacturing processes described in the BLA and those used for other licensed parenteral products at Cilag AG. These processes were inspected last year with no significant regulatory findings".

The drug substance manufacturing facility (Centocor Biologics in St. Louis, MO) was inspected on April 14-18, 2008 (FEI Number 3003418999) and Inspectional Observations (SF483) were noted. The resolution of these inspectional observations is unknown.

I concur with the recommendation from DMA that the product is not ready for approval based upon quality problems. The quality problems should be resolved and the consequences, if any, of inspectional observations at the drug substance manufacturing facility should be resolved prior to approval.

## **4. Nonclinical Pharmacology/Toxicology**

Due to the mechanism of action of ustekinumab, inhibition of IL-12/IL-23 expression, there is a biologic plausibility for enhanced carcinogenic risk. Formal two-year systemic carcinogenicity studies have not been conducted with ustekinumab. However, adequate literature data is available to indicate that inhibition of IL-12/IL-23 expression leads to an increased carcinogenic risk. Systemic administration of IL-12 exhibits an anti-tumor effect in mice, inhibition of IL-12/IL-23 expression with a murine monoclonal antibody enhances tumor formation in mice challenged with squamous cell carcinoma cells and removal of the IL-12/IL-23 gene in knockout mice enhanced tumor formation in mice. There is sufficient nonclinical data in the literature indicating an increased carcinogenic risk with inhibition of IL-12/IL-23 expression to justify inclusion in labeling of this animal data to inform prescribers about the potential carcinogenic risk from ustekinumab use.

I concur with the conclusions reached by the pharmacology/toxicology reviewer and supervisors that there are no outstanding pharm/tox issues that preclude approval. The labeling of Ustekinumab should use the information from the nonclinical studies conducted by the sponsor and from the literature as outlined by the reviewer. A potential increased carcinogenicity risk may be associated with the chronic use of ustekinumab in psoriasis patients.

## 5. Clinical Pharmacology/Biopharmaceutics

**Biopharmaceutics:** Clinical data suggest “decreased efficacy in antibody-positive subjects, however the data are inadequate for conclusions. The biopharmaceutics reviewer is recommending an in-vitro study (or studies) to determine whether IL-12 and/or IL-23 modulate CYP enzyme expression and whether Ustekinumab is able to reverse the effects of IL-12/IL-23 on CYP expression (e.g., in vitro hepatocyte study). An alternative in vivo approach would be to determine the potential of Ustekinumab for the alteration of CYP substrate metabolism in psoriasis patients (e.g., a cocktail study with CYP probe drugs).

**Pharmacogenomics:** I concur with the recommendation of the pharmacogenomics reviewer that early identification of non-responders through the use of biomarkers would benefit clinicians and patients, and that the sponsor should continue to search for efficacy biomarkers.

**Pharmacometrics:** The applicant has proposed weight based dosing in two increments, with patients weighing < 100kg receiving 45mg initially and 4 weeks later, followed by dosing every 12 weeks. Patients >100kg would receive 90mg initially and 4 weeks later, followed by dosing every 12 weeks. The Pharmacometrics reviewer has recommended an alternative 3 step dosing, with patients weighing <70kg (154 lbs) receiving 45mg initially and 4 weeks later, followed by dosing every 12 weeks. For patients  $\geq$  70kg and < 100kg (220 lbs) the recommended dose is 67.5mg initially and 4 weeks later, followed by dosing every 12 weeks. For patients weighing  $\geq$ 100kg, the recommended dosing would remain unchanged from the applicant proposal (90 mg initially and 4 weeks later, followed by dosing every 12 weeks). The Advisory Committee voted 7 vs. 3 to recommend the two step dosing as originally proposed by the applicant. The main concerns from the committee were (1) lack of data at 67.5 mg (2) possible delays in generating stability data for 67.5 mg and (3) lack of availability of

information on the lowest effective dose. However, there was some interest in this alternative dosing regimen and this should be explored more fully by the sponsor. The sponsor did not pursue substantive dose ranging studies for this product. At this time I concur with the clinical reviewer and the majority of the Advisory Committee that weight based dosing in two increments is appropriate for initial approval. Additional dosing regimens could be explored post marketing.

The labeling recommendations for pharmacometrics, drug-drug interactions and pharmacogenomics will be considered prior to approval of the application.

## **6. Clinical Microbiology**

No clinical microbiology review was provided.

## **7. Clinical/Statistical-Efficacy**

I concur with the conclusions of the primary medical officer that the applicant has provided sufficient evidence of efficacy. The applicant conducted two adequate and well-controlled Phase 3 studies, in which primary efficacy was assessed at Week 12 by the proportion of subjects who achieved a 75% reduction in the Psoriasis Area Severity Index (PASI 75). A major secondary endpoint was the Physician's Global Assessment (PGA). The Phase 3 studies provided substantial evidence of efficacy of ustekinumab in the target population of patients with moderate to severe plaque psoriasis. In both studies, efficacy was demonstrated for both doses on the PASI and on the PGA. Efficacy outcomes were generally similar between dosing groups and across studies. Both doses were proven efficacious in both weight categories; however, higher efficacy outcomes were observed in heavier subjects (> 100 kg) who received 90 mg of ustekinumab compared to those who received 45 mg. Efficacy was demonstrated in sub-groups.

## **8. Safety**

The assessment of safety was based primarily on the integrated analyses of data from three studies (a Phase 2 study and the Phase 3 studies). In the reviewer's opinion, the applicant provided substantial evidence of the safety of ustekinumab in the target population through 18 months of exposure. Overall rates and patterns of serious adverse events suggested no increased risk when ustekinumab-treated subjects were compared to placebo-treated subjects or to each other (i.e., 45 mg compared to 90 mg). This conclusion held when specific categories of events were considered, including serious cardiac events, serious infections, serious malignancies, and serious nervous system disorders. Overall rates for treatment-emergent adverse events were generally similar between all treatment groups, and generally suggested no dose response when ustekinumab groups were compared (the most common

adverse events were nasopharyngitis and upper respiratory tract infection). Adverse drug reactions were not worrisome in pattern or frequency of occurrence.

The safety database revealed no signals suggesting that patients with pharmacologic blockade of IL-12/IL-23 might manifest the vulnerabilities to the narrow spectrum of infections seen in individuals genetically deficient in these cytokines. Specifically, there were no reports of infections by nontuberculous mycobacteria or of salmonella. There was one report of a serious gastroenteritis, and the subject's presentation and clinical course did not suggest salmonellosis. Of note, 68 subjects with latent tuberculosis diagnosed during screening were enrolled in the trials (with appropriate treatment initiated either prior to or simultaneous with first administration of study agent), and all were at some point exposed to ustekinumab because of the crossover design of the Phase 3 studies. Two additional subjects were diagnosed with latent tuberculosis post-screening. Through the end of the reporting, there were no reports of complications from tuberculosis.

The safety database did not signal that the malignancy risk suggested in animal models might be translating to humans; however, a signal of this sort might not be revealed in a database in which the maximum duration of follow-up was through 18 months, with 373 ustekinumab-exposed subjects followed through this period. Similarly, the database might not be of sufficient size to detect low frequency events (infectious or malignant). Therefore, the available data permit only tentative conclusions regarding these risks, and additional, longer-term data are needed to assess for these theoretical risks in patients treated with ustekinumab.

Consultation was obtained from the Office of Surveillance and Epidemiology concerning the risk assessment and risk mitigation needs for ustekinumab. I concur with the consensus reached by the OSE reviewers, the primary clinical reviewer, and the cross discipline team leader that if approved, specific labeling and a REMS consisting of a Medication Guide and Communication plan are necessary to emphasize the potential risks of infection and malignancy. I concur with the conclusion of the clinical reviewer that a mandatory registry is not necessary for assessment of a theoretical risk (as opposed to management of a known serious risk) and that no signal emerged in the safety database to merit a mandatory registry. However, a REMS should be required which provides "strong educational information to patients and physicians". The risk management program should be reevaluated in the presence of new data.

The theoretical risk of malignancy should be a concern for all parties involved in the review of ustekinumab for the treatment of psoriasis. This risk was extensively discussed before the DODAC on 6/17/08 with a focus on the need for complete ascertainment and long-term assessment of cancer events. I am in concurrence with the OSE consultant's conclusions concerning the utility of exposure registry information. The utility of these registries for identification of malignancy risk (or any other risk) while reasonable and prudent is simply unknown to us. While it has been suggested that additional controlled clinical trials of ustekinumab may offer a more robust buttress for malignancy risk assessment than exposure registry observational studies, it is unclear how these studies would be designed and conducted and whether the potential signal in the animal data is sufficient to mandate what could become decades of premarketing trials. A disease specific registry, managed outside FDA (possibly

NIH) and not limited to one marketed psoriasis treatment, may be a more optimal vehicle for obtaining adverse event information.

TRADENAME (ustekinumab) is an immunosuppressant to be used chronically in psoriasis patients. Potential adverse events that may be related to the use of TRADENAME (ustekinumab) include serious infections and malignancy. Based on data from rodent models, there is a theoretical concern that blockade of IL-12/IL-23 may heighten patients' risk for malignancy. Humans genetically deficient in IL-12/IL-23 appear to have particular susceptibilities to infections from BCG, environmental mycobacteria and non-typhoidal salmonella but no apparent excess risk for malignancy, although most of these patients have yet to reach middle age. There are no apparent signals for particular infection susceptibilities or malignancy in the safety database for TRADENAME (ustekinumab) submitted in support of the BLA; however, follow-up is only through 18 months.

I recommend that REMS is necessary for this biologic drug product to ensure that the benefits of the drug outweigh the risks. Post-marketing clinical trials will be needed to further assess these risks of serious infection and malignancy.

The REMS should contain both a medication guide and a communication plan.

The medication guide should be developed as provided for under 21CFRPart 208.

The communication plan must include, at minimum, the following:

- Dear Healthcare Provider Letters to be distributed to dermatologists and other specialties expected to treat infectious and oncologic complications potentially associated with TRADENAME (ustekinumab), if the application is approved. This letter should also inform prescribers about any available registries which may enroll patients treated with TRADENAME (ustekinumab).
- An intensive adverse event reporting awareness campaign at major national meetings of appropriate specialties; if possible, develop and provide free-of-charge targeted CME programs covering the basic science underlying recommendations about infectious complications and the need for cancer surveillance.
- A description of the audience for the communication plan, stating specifically the types and specialties of healthcare providers to whom the communication materials will be directed. These should include non-prescribers in specialties likely to be consulted for infectious or malignant adverse events.
- A schedule for when and how these letters/materials are to be distributed to healthcare providers at the time TRADENAME (ustekinumab) is approved, and at specified intervals thereafter, if this application is approved.

**Timetable for Assessments:** The proposed REMS must include a timetable for assessment of the REMS that shall be no less frequent than by 18 months, by 3 years and in the 7th year after the REMS is approved.

The applicant should specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. The assessments should be submitted within 60 days of the close of the interval.

The applicants REMS assessments must assess the extent to which the elements of the REMS are meeting the goals of the REMS and whether modifications to the elements or goals are needed.

The proposed REMS submission should include two parts: a "Proposed REMS" and a "REMS Supporting Document." The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Information needed for assessment of the REMS may include but may not be limited to:

1. Results of evaluations addressing:
  - a. Prescribers' understanding of TRADENAME (ustekinumab) risks, including the risk of serious infection and malignancy, and how to select patients who appropriate for treatment
  - b. Patients' understanding of the risks of TRADENAME (ustekinumab), including the risks of serious infection and malignancy
  - c. Who is performing the TRADENAME (ustekinumab) injection in the healthcare setting (i.e., the physician/prescriber, nurse, patient, other)
  - d. How often patients are examined during TRADENAME (ustekinumab) therapy by a healthcare professional, and the type of professional (i.e., physician/prescriber, physician/non-prescriber, nurse, other)
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective actions to address non-compliance.
4. Report on the content, participation, and effectiveness of CME programs targeting prescribers and oncologists.
5. A summary of all reported serious infections and malignancies, with analysis of adverse event reporting by prescriber type (e.g., dermatologist, nurse, internist, oncologist).
6. Based on the information submitted, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

#### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

The applicant should evaluate the safety and efficacy of long-term continuous use of ustekinumab in the PHOENIX1 and PHOENIX2 trials through 5 years from initial administration of product (264 weeks).

### **POSTMARKETING STUDY COMMITMENTS**

I concur with the recommendations for post marketing study commitments including:

1. The applicant further evaluates maintenance dosing (less frequent dosing, lower doses).
2. The applicant conduct an in vitro study or studies to determine whether IL-12 and/or IL-23 modulate CYP enzyme expression and whether ustekinumab is able to reverse the effects of IL-12/IL-23 on CYP expression (e.g., in vitro hepatocyte study). An alternative in vivo approach would be to determine the potential of ustekinumab for the alteration of CYP substrate metabolism in psoriasis patients (e.g., a cocktail study with CYP probe drugs).
3. The applicant develops an assay with which the presence of ustekinumab does not interfere.
4. Conduct a prospective, multi-center registry of 4,000 adult psoriasis patients treated with Stelara in the United States, followed for eight years
5. Conduct a prospective, 5 year observational study of adverse events observed in clinical practice (Nordic Database Initiative)
6. Conduct a prospective, observational pregnancy exposure registry in the U.S.
7. Conduct a lactation study

## **9. Advisory Committee Meeting**

The Dermatologic and Ophthalmologic Drugs Advisory Committee met on 27 June 2008 to consider this application. The Committee was asked to provide specific advice and recommendations on a) the dosing regimen b) carcinogenicity c) long-term safety and d) self-administration. Following substantial discussions, the Committee voted unanimously that the applicant had provided sufficient information to demonstrate efficacy, and to support the dosing schedule of every 12 weeks. In addressing the dosing regimen, the majority of the committee (7-3) voted for the two doses due to the fact that the 45mg and 90mg dose was studied by the sponsor. Members voting for a third dose (67.5mg) felt the population weighing between 70kg and 100kg would have an increased risk of side effects and toxicity if given the 90mg dose. The Committee advised (Yes 1, No 10) that the applicant had not provided sufficient information to inform patients and physicians regarding how/when to stop treatment with Ustekinumab. They also advised that the database provided was not fully sufficient in either length of time or number of subjects to fully characterize the critical safety concerns.

The Committee voted 11-0 that they were concerned about the potential malignancy risk associated with this class of products, that this was important information to convey to prescribers, but that additional animal studies were not needed.

The Committee voted unanimously for approval without additional premarket studies, and voted unanimously that the applicant's risk assessment proposals (PSOLAR, 5 year extension of pivotal trials) was not sufficient to characterize the long term safety.

## 10. Pediatrics

Pediatric use has not been evaluated. Pediatric study requirements were discussed at the PERC on 10Dec2008. All studies will be deferred as the adult studies are complete and approval is anticipated once the deficiencies are corrected.

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

b(4)

The overall pediatric plan continues under discussion and will be further described prior to approval.

## **11. Other Relevant Regulatory Issues**

There are no other unresolved relevant regulatory issues.

## **12. Labeling**

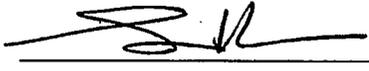
**Proprietary Name:** The applicant original proposal of Stelara was reviewed by DMETS and found to be unacceptable because of its orthographic similarity to Stalevo, a product marketed in the US for treatment of idiopathic Parkinson's disease. The applicant submitted a request for reconsideration and DMEPA recommends approval of the proprietary name Stelara.

Physician labeling, patient labeling and container carton continue under review. A medication guide will be requested in the Risk Evaluation and Management Plan.

## **13. Decision/Action/Risk Benefit Assessment**

- Recommendation for Regulatory Action – Complete Response
- Risk Benefit Assessment -An assessment of risk benefit for this product will be completed following submission and review of the REMS.
- Recommendation for Postmarketing Risk Management Activities -The applicant should provide a REMS consisting of a Medication Guide and Communication plan as described above.
- Recommendation for other Postmarketing Study Commitments – These will be conveyed with the approval action.

Division Director Review

 12/16/02

Susan J. Walker, M.D.  
Director  
Division of Dermatology and Dental Products

## Cross-Discipline Team Leader Review

<b>Date</b>	15 December 2008
<b>From</b>	Jill Lindstrom, MD <i>Jill Lindstrom 12.15.08</i>
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>BLA #</b>	125261
<b>Applicant</b>	Centocor Biologics, LLC
<b>Date of Submission</b>	13 January 2007
<b>PDUFA Goal Date</b>	28 December 2008
<b>Proprietary Name / Established (USAN) names</b>	Stelara/ustekinumab
<b>Dosage forms / Strength</b>	Sterile parenteral solution; 45mg/0.5mL, 90 mg/1mL
<b>Proposed Indication(s)</b>	Treatment of moderate to severe psoriasis
<b>Recommended:</b>	<i>Complete Response</i>

### 1. Introduction

This CDTL memo will summarize the findings of the multi-disciplinary review team, highlight the areas (CMC, post-marketing risk mitigation) that generate the recommendation for a *Complete Response*, and provide my recommendation regarding dosing regimen.

### 2. Background

Ustekinumab is a novel, first-in-class, fully human monoclonal antibody against the shared p40 subunit common to both interleukin-12 (IL12) and interleukin-23 (IL23). It has been developed for the treatment of moderate to severe psoriasis.

### 3. CMC/Device

Stelara is supplied as a sterile, single-use, 2mL stoppered glass vial containing either 45mg or 90 mg ustekinumab and sucrose, histidine, and polysorbate 80. Stelara contains no preservative. The drug substance and drug product are manufactured at Centocor St. Louis. Preapproval inspection issues were resolved during the review cycle. Stability was set at ██████████ when stored at 2° – 8° C and protected from light. The initial recommendation of the Product Quality team was for approval. b(4)

However, updated product stability data submitted in August and October, 2008, revealed an unexpected increase in visible particulates for product produced in 2008. Three of four lots failed to meet the release standard for visible particulate assay, and the remaining lot showed an atypical increase over time. The applicant attributed the out-of-specification findings to a change in the assay ████████████████████ glass syringes ████████████████████. The revised assay procedure had been validated, however, and increases in visible particulates was not observed with assay qualification and validation. In addition, conflicting data was obtained during stability testing of other samples. Because the root cause of the most recent increase in visible particulates is not clear, the Product Quality team issued an amended review b(4)

recommending a *Complete Response* until the issues are resolved and product potency and purity can be assured.

#### **4. Nonclinical Pharmacology/Toxicology**

As their pivotal chronic toxicology study, the applicant conducted a 26-week subcutaneous dose study in cynomolgus monkeys with a 12-week recovery period. Toxicokinetic evaluation confirmed high exposures in excess of that required for complete pharmacologic inhibition of IL12/23 activity. One of ten monkeys developed bacterial enteritis; no other significant adverse events were noted. Histopathology did not reveal pre-neoplastic change in any organs.

Genotoxicity studies, which are not typically conducted with monoclonal antibodies due to their large size, were not conducted with ustekinumab.

The applicant submitted literature studies in lieu of conducting carcinogenicity studies. The literature studies, reviewed comprehensively by Dr. Jiaqin Yao and also in the OSE consult of October 28, 2008 (section 3.1.1), suggest that ustekinumab may present a risk for carcinogenicity. Briefly, administration of murine IL12 had an anti-tumor effect against transplanted tumors in mice, and IL12/IL23p40 knock-out mice had reduced anti-tumor host defenses, manifested as earlier development, increased frequency, and greater aggressiveness of UV-induced tumors. Both the Pharmacology/Toxicology team and the Advisory Committee recommended communication in labeling of this signal for potential risk, but did not recommend additional nonclinical carcinogenicity studies.

Stelara did not reduce male fertility in cynomolgus monkeys, although the group size was small, and an analogous murine anti-IL12/IL23p40 antibody did not reduce female fertility in mice. Teratogenicity was not observed. Embryofetal toxicity studies in cynomolgus monkeys demonstrated similar rates of fetal loss between treated and untreated animals; one neonatal loss was seen in each of two dose groups but none in control animals. Proposed wording to communicate this information has been incorporated into draft labeling.

There are no outstanding nonclinical pharmacology/toxicology issues. The Pharmacology/Toxicology team recommended an approval action from the nonclinical perspective. No nonclinical postmarketing studies are recommended or required.

#### **5. Clinical Pharmacology/Biopharmaceutics**

Stelara is a liquid-in-vial dosage form intended for subcutaneous injection administered initially in two doses four weeks apart followed by repeat dosing every 12 weeks. The median time to reach the maximum serum concentration ( $t_{max}$ ) in subjects with psoriasis was 13.5 days and 7 days respectively after a single subcutaneous administration of 45 mg and 90 mg of ustekinumab. The median half-life ( $t_{1/2}$ ) of ustekinumab was approximately 3 weeks in psoriasis subjects, ranging from 15 to 32 days across all psoriasis studies.

The applicant studied two doses, 45mg and 90mg, in their pivotal trials, which included population pharmacokinetics. Serum concentration was inversely proportional to body weight; serum concentrations for heavier subjects were lower than for lighter subjects. The applicant performed an exposure-response analysis which identified a clear dose-response: both IGA and PASI 75 correlated with serum concentration or AUC. For a given dose, subjects lighter than 100kg demonstrated a better response than subjects heavier than 100kg. The applicant based their dosing paradigm, 45mg for patients less than 100kg and 90 mg for patients  $\geq 100$ kg, on this analysis.

Dr. Pravin Jadhav conducted a pharmacometric analysis to determine whether the applicant's proposal represented the best dosing regimen; the reader is referred to his and Dr. Abi Adebowale's reviews for full discussion. The applicant studied two doses, 45mg and 90mg, across all body weights. Both doses demonstrated effectiveness, although the higher dose was more effective in heavier subjects. Dose-response was not seen for adverse events. Using pharmacometric modeling, six dosing paradigms were explored: 45mg for all, 90 mg for all, the applicant's two-step proposal, a three-step proposal, a five-step proposal, and a semi-continuous proposal. The results are presented in Table 1.

Table 1: Predicted response rates under different dosing regimens based on the AUC-proportion of PASI75 responders model

Dosing strategy	Dose	Predicted Response Rate (%) (Overall and by weight cut-offs)			
		Overall	<70kg	70-<100kg	$\geq 100$ kg
1 dose for all	45mg	65	80	68	54
1 dose for all	90mg	75	84	76	70
<b>Weight-based dosing adjustments</b>					
2-step	<100kg: 45mg $\geq 100$ kg: 90mg	<b>70</b>	80	<b>68</b>	70
3-step	<70kg: 45mg 70kg-<100kg: 67.5mg(0.75mL) $\geq 100$ kg: 90mg	<b>73</b>	80	<b>74</b>	70
5-step	<45kg: 45mg 45kg-<60kg: 54mg(0.6mL) 60kg-<75kg: 67.5mg(0.75mL) 75kg-<90kg: 81mg(0.9mL) $\geq 90$ kg: 90mg	75	82	75	70
Semi-continuous	<45kg: 45mg 45kg-90kg: 1mg/kg $\geq 90$ kg: 90mg	75	82	75	70

Source: adapted from Pharmacometrics Review (31 July 2008), BLA 125261, Dr. Pravin Jadhav, pp.29-30.

The dosing paradigms were presented to the Advisory Committee, who voted as follows:

- 2-step dosing: 7 votes
- 3-step dosing: 3 votes
- abstain: 1 vote

The committee expressed the following concerns about the 3-step paradigm: (1) lack of data at 67.5 mg (2) possible delays in generating stability data for 67.5 mg and (3) lack of availability of information on the lowest effective dose. Regarding the first concern, lack of data at 67.5mg, the applicant provided safety and effectiveness data that fully bracket this dose. Regarding the second concern, delays in generating stability data for the 67.5mg dose, it appears that the committee members did not realize that the 3-step regimen would not require a production of 67.5mg vial prior to marketing; the applicant could market their proposed dose configurations, 45mg and 90mg, and prescribers could use the 90mg vial for patients receiving either the 67.5mg dose or the 90mg dose until stability data allowed marketing of a 67.5mg vial. The third concern, the lack of information regarding the lowest effective dose, reflects the desire for dose optimization for the small minority of patients who weigh less than 45kg; this concern, when applied to the much larger population of patients who weigh 70-100kg, *supports* the 3-dose paradigm, which would optimize the dose for this much larger segment of the population in whom the drug will be used.

Because of the clear exposure-response relationship for effectiveness, the bracketing provided by the safety and effectiveness data from the 45mg and 90mg doses, and the absence of dose-response for adverse events at these doses, I concur with the recommendation of the Clinical Pharmacology team for a three-step dosing regimen.

b(4)

---

The applicant did not conduct a thorough QT/QT<sub>c</sub> study. The CDER DCRP QT Interdisciplinary Review Team (QT-IRT) advised that no such study was needed because ustekinumab, as a monoclonal antibody, could not access the hERG pore via the intracellular side, and QT prolongation has not been observed with any other monoclonal antibody.

Ustekinumab is not metabolized by CYP450 enzymes. However, because the formation of CYP450 enzymes can be altered by increased levels of cytokines during chronic inflammation, a molecule such as ustekinumab that antagonizes cytokine activity may affect the formation of CYP450 enzymes. This potential effect and resulting need to monitor concomitant medications upon initiation of Stelara should be addressed in labeling. Additionally, the Clinical Pharmacology team recommended the following postmarketing commitment:

Conduct an in vitro study or studies to determine whether IL-12 and/or IL-23 modulate CYP enzyme expression and whether ustekinumab is able to reverse the effects of IL-12/IL-23 on CYP expression (e.g., in vitro hepatocyte study). An alternative in vivo approach would be to determine the potential of ustekinumab for the alteration of CYP substrate metabolism in psoriasis patients (e.g., a cocktail study with CYP probe drugs).

## 6. Clinical Microbiology

Not applicable

## 7. Clinical/Statistical- Efficacy

The applicant submitted data from two pivotal trials, T08 and T09, to establish the effectiveness of Stelara, either 45mg and 90mg, in the treatment of moderate to severe psoriasis in patients who are candidates for phototherapy or systemic therapy. Subjects were dosed on week 0, week 4, and then every 12 weeks after that. The trials, which are ongoing, are similar in design (identical through week 28) and will follow subjects for five years. The primary timepoint was at 12 weeks, after which subjects on placebo were crossed-over to active treatment. The primary efficacy endpoint was PASI75, and a major secondary endpoint was Clear or Minimal on the Physician's Global Assessment Scale. The results for the above endpoints for both T08 and T09 are presented in the table below:

Table 2: Week 12 Efficacy Results

	Stelara 45 mg	Stelara 90 mg	Placebo
<b>Study 08</b>	N=255	N=256	N=255
PASI 75 response	171 (67%) p<0.001	170 (66%) p<0.001	8 (3%)
PGA Cleared/Minimal	154 (60%) p<0.001	158 (62%) p<0.001	10 (4%)
<b>Study 09</b>	N=409	N=411	N=410
PASI 75 response	273 (67%) p<0.001	311 (76%) p<0.001	15 (4%)
PGA Cleared/Minimal	278 (68%) p<0.001	302 (73%) p<0.001	20 (5%)

Source: Biostatistical Review (28 July 2008), BLA 125261, Dr. Kathleen Fristch, pp.31.

The BLA included data to week 52 for T08 and to week 28 for T09. The reader is referred to the reviews by Drs. Brenda Carr and Kathleen Fritsch for a full discussion of the trial designs and results.

The results from T08 and T09 demonstrate that Stelara is superior to placebo in the treatment of moderate to severe psoriasis. I concur with the conclusions of Clinical reviewer and Biostatistical team that the data support a determination of effectiveness for both doses.

## 8. Safety

The safety database, comprised of pooled data from the two pivotal studies and a phase 2 study and including 2,226 ustekinumab-exposed subjects, 372 of who received ustekinumab for at least one year, is adequate to characterize adverse events. Four deaths were reported, three of which were determined to be unlikely due to ustekinumab exposure; the fourth death occurred in a subject with metastatic kidney (transitional cell) cancer, and relatedness to ustekinumab was considered possible. The rates of serious and non-serious adverse events were similar across all arms. The most frequently reported adverse events were nasopharyngitis and respiratory infection. Laboratory parameters were generally comparable across ustekinumab and placebo-treated groups. No effect of ustekinumab on lymphocyte parameters was identified.

No cases of active tuberculosis or non-tuberculous mycobacterial infection were reported. Of note, diagnosis of latent tuberculosis did not preclude enrollment if the subject initiated treatment; 68 such subjects were enrolled. No cases of systemic fungal infection or salmonellosis were reported.

The rate of injection site reactions was low, and no cases of anaphylaxis or serum sickness were reported. Immunogenicity rates were relatively low; however, the presence of ustekinumab interfered with antibody assessment in a large proportion of subjects.

Eight solid malignancies (prostate [two], kidney, thyroid, breast, colon, tongue, and malignant melanoma in situ) were reported in 8 subjects, fewer than would be expected by comparison with the SEER database (per subject year exposure, adjusted for age, gender and race). No lymphomas were reported. Eighteen ustekinumab-treated subjects developed nonmelanoma skin cancer: 5 squamous cell carcinomas and 14 basal cell carcinomas. The rate and types of solid tumor malignancies, as well as the ratio of basal to squamous cell carcinomas of the skin, do not suggest a malignancy signal related to immunosuppression.

Cardiovascular events were uncommon, and rates were not increased over expected background rates.

The applicant did not provide sufficient data to establish the safety of self-administration. Subjects were permitted to administer self-administer study agent after the second dose, however this took place at the study site under observation by study personnel. Unsupervised self-administration at home was not permitted. Because the infrequency of dosing could impede mastery of injection technique, it will be important to understand the impact of true self-administration (at home, without study personnel oversight) on safety and effectiveness and to ascertain whether subjects are able to successfully self-administer the drug without the benefit of professional oversight.

## **9. Advisory Committee Meeting**

The application was presented to the Dermatologic and Ophthalmologic Drugs Advisory Committee on June 17, 2008. The Committee unanimously agreed that the applicant had demonstrated the effectiveness of ustekinumab in the treatment of psoriasis and had provided sufficient information to support the dosing regimen, and the committee unanimously recommended approval. The committee also expressed unanimous concern about the potential for malignancy demonstrated by nonclinical studies and unanimously recommended that these findings be communicated to prescribers. The committee unanimously agreed that subjects had been followed for an insufficient amount of time, and were in near unanimous agreement that an insufficient number of subjects had been studied. The committee's vote regarding a two-step or three-step dosing paradigm is presented in section 5 of this review. The committee voted 4 (for) to 7 (against) against self-administration. The committee unanimously agreed that the applicant's risk assessment proposals were insufficient.

## 10. Pediatrics

The applicant conducted studies in subjects 18 years of age and older. The applicant's pediatric assessment included a request for deferral for all pediatric populations. The

\_\_\_\_\_

\_\_\_\_\_

b(4)

adolescents and adults. The deferral request and pediatric plan were presented to the Pediatric Review Committee; the committee concurred with the deferral request and the proposed plan.

## 11. Other Relevant Regulatory Issues

DSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted.

## 12. Labeling

Review by the Division of Medical Error Prevention and Analysis found the proposed tradename, Stelara, to be acceptable.

The multidisciplinary review team revised the draft professional labeling provided by the applicant, but did not engage in labeling negotiations with the applicant. At the time of close of this review, the draft professional labeling does not reflect the 3-step dosing paradigm recommended by the Clinical Pharmacology team and this reviewer.

A Medication Guide is necessary but was not provided.

## 13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: *Complete Response*

### Risk Benefit Assessment

The applicant demonstrated the effectiveness of their product for the treatment of moderate to severe psoriasis in patients who are candidates for phototherapy or systemic therapy. No clear safety signals for infection, malignancy, cardiovascular events, or immunogenicity emerged during the development program. The applicant studied sufficient numbers of subjects to adequately characterize common adverse events. However, because of the chronic nature of psoriasis and the consequent likelihood of long-term use of Stelara, as well as the theoretical concern for infectious or malignant adverse events based the mechanism of action of the drug, a multi-pronged approach to postmarketing risk assessment is needed to elucidate potential low-frequency or long-latency signals. Additionally, because of the potential (but not documented) risks, health care provider and patient education regarding potential risks, mitigation measures, and the need for adverse event reporting will be needed. The applicant proposed additional risk assessment via 5-year continuation of pivotal trials T08 and T09

(ongoing), continuation of a 64-week, active-comparator trial against etanercept, addition of a ustekinumab arm to the existing PSOLAR postmarketing registry for serious adverse events, a prospective 5-year observational cohort study (Nordic Database Initiative), a 5-year pregnancy registry, and datamining, in addition to routine pharmacovigilance. The applicant proposed a specialty pharmacy provider to address prescriber and patient education. In addition to the applicant's proposals, the OSE review team recommended implementation of a REMS, consisting of a Medication Guide and a Communication plan, as well as labeling for prescriber administration and including malignancy and serious infections as 15-day reportable adverse events.

#### Recommendation for Postmarketing Risk Management Activities

The applicant should provide a REMS comprised of a Medication Guide, Communication Plan, and a timetable for planned assessments. Elements to assure safe use, such as restricted distribution, are not needed. A mandatory registry, which would comprise restricted distribution for the purpose of risk assessment, is not recommended as it would be untenable from ethical, regulatory, and legal standpoints.

#### Recommendation for other Postmarketing Study Commitments

1. Conduct in vitro study or studies to determine the effect of IL12/IL23 on CYP expression and whether ustekinumab reverses that effect.
2. Develop an assay with which the presence of ustekinumab does not interfere.
3. Evaluate the safety and effectiveness of long-term continuous use of ustekinumab in the ongoing studies T08 and T09
4. Conduct studies to evaluate the maintenance dosing, to include less frequent dosing.
5. Conduct a prospective, multi-center registry of 4000 adults psoriasis patients treated with Stelara in the United States, followed for 8 years.
6. Conduct a prospective, 5-year observational study of adverse events observed in clinical practice (Nordic Database Initiative).
7. Conduct a prospective, observational pregnancy exposure registry in the US that compares the pregnancy and fetal outcomes of women exposed to ustekinumab during pregnancy to an unexposed control population.
8. Conduct a lactation study in women who are breastfeeding while being exposed to ustekinumab to assess the presence of ustekinumab in breast milk and potential effects in nursing infants.
9. Pending absence of significant safety signals in adults, conduct dose range finding and safety and efficacy studies in pediatric subjects.
10. Commit to expedited (15-day) reporting of spontaneous adverse event reports of malignancy or serious infections (including, but not limited to, opportunistic infections, tuberculosis, salmonellosis, diverticulitis).

#### Recommended Comments to Applicant

#### PRODUCT QUALITY

Deficiencies:

1. Control procedures need to be established to validate the performance of manufacturing processes responsible for causing variability in the drug product (§ 211.110). Specifically, numerous drug product lots have recently failed the visible particulate matter assay specification at release and during stability testing. The application lacks documentation of an event that can reasonably be determined to have caused the visible particulate assay out-of-specification (OOS) results.
2. The application lacks an accurate testing and sampling method for measurement of visible particulate matter that has been developed, documented, reviewed, and approved by Centocor's Quality Control Unit (§ 211.165).

Information Needed for Resolution:

1. Identification of the root cause of the OOS results for the visible particulate assay supported by a comprehensive, consistent narrative of the investigation into the OOS events with data that strongly and directly support the conclusions. The root cause investigation should also outline corrective actions taken that assure consistent drug product manufacture and testing.
2. Development and validation of a robust sampling and testing method for assessment of the level of visible particulates in the drug product. Development and validation results should provide assurance that the assay is able to consistently and reproducibly perform its intended function. The assay should be reviewed and approved by Centocor's Quality Control Unit.

Additional Requests and Comments:

1. Provide an analysis of the impact of changes to the sampling method for other assays which used pooled material, such as the sub-visible particulate method.
2. The IEF and cIEF assays need to be run side-by-side until sufficient data have been submitted to the Agency to demonstrate that the cIEF assay is as stability indicating as the IEF assay. These data should demonstrate that the cIEF assay would result in failures for stressed and accelerated stability samples at or before failures would occur due to the appearance of faint acidic bands seen by IEF method.
3. Both working cell banks \_\_\_\_\_, are suitable for use in manufacturing. b(4)

CLINICAL

You must submit a proposed REMS, as described below.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Food Drug and Cosmetic Act (FDCA) to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing

studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)) and to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

Stelara (ustekinumab) is an immunosuppressant to be used chronically in psoriasis patients. Potential adverse events that may be related to the use of Stelara (ustekinumab) include serious infections and malignancy. Based on data from rodent models, there is a theoretical concern that blockade of IL-12/IL-23 may heighten patients' risk for malignancy. Humans genetically deficient in IL-12/IL-23 appear to have particular susceptibilities to infections from BCG, environmental mycobacteria and non-typhoidal salmonella but no apparent excess risk for malignancy, although most of these patients have yet to reach middle age. There are no apparent signals for particular infection susceptibilities or malignancy in the safety database for Stelara (ustekinumab) submitted in support of the BLA; however, follow-up is only through 18 months.

After consideration of this information, we have determined that a REMS is necessary for the drug to ensure that the benefits of the drug outweigh the risks, and we have determined that postmarketing clinical trials will be needed to further assess these risks.

#### RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Stelara (ustekinumab) to ensure that the benefits of the drug outweigh the potential risks of serious infection and malignancy. The REMS, once approved, will create enforceable obligations.

Your proposed REMS must contain the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Stelara (ustekinumab) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Stelara (ustekinumab). FDA has determined that Stelara (ustekinumab) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Stelara (ustekinumab). FDA has also determined that Stelara (ustekinumab) is a product for which patient labeling could help prevent serious adverse events. Under 21 CFR 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who receive Stelara (ustekinumab) injections.

**Communication Plan:** We have determined that a communication plan to healthcare providers who are likely to prescribe and/or inject Stelara (ustekinumab) will support implementation of the elements of your REMS. The communication plan must include the dissemination of information about the potential risks of serious infection and malignancy.

The communication plan must include, at minimum, the following:

- Dear Healthcare Provider Letters to be distributed to dermatologists and other specialties expected to treat infectious and oncologic complications potentially associated with Stelara (ustekinumab), if the application is approved. This letter should also inform prescribers about any available registries which may enroll patients treated with Stelara (ustekinumab).
- An intensive adverse event reporting awareness campaign at major national meetings of appropriate specialties; if possible, develop and provide free-of-charge targeted CME programs covering the basic science underlying recommendations about infectious complications and the need for cancer surveillance.
- A description of the audience for the communication plan, stating specifically the types and specialties of healthcare providers to whom the communication materials will be directed. These should include non-prescribers in specialties likely to be consulted for infectious or malignant adverse events.
- A schedule for when and how these letters/materials are to be distributed to healthcare providers at the time Stelara (ustekinumab) is approved, and at specified intervals thereafter, if this application is approved.

**Timetable for Assessments:** The proposed REMS must include a timetable for assessment of the REMS that shall be no less frequent than by 18 months, by 3 years and in the 7th year after the REMS is approved.

We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the interval.

Your REMS assessments must assess the extent to which the elements of your REMS are meeting the goals of your REMS and whether modifications to the elements or goals are needed.

We suggest that your proposed REMS submission include two parts: a "Proposed REMS" and a "REMS Supporting Document." Attached is a template for the Proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Stelara (ustekinumab). Additionally, all relevant proposed REMS materials including educational and communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS.

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Information needed for assessment of the REMS may include but may not be limited to:

1. Results of evaluations addressing:
  - a. Prescribers' understanding of Stelara (ustekinumab) risks, including the risk of serious infection and malignancy, and how to select patients who appropriate for treatment
  - b. Patients' understanding of the risks of Stelara (ustekinumab), including the risks of serious infection and malignancy
  - c. Who is performing the Stelara (ustekinumab) injection in the healthcare setting (i.e., the physician/prescriber, nurse, patient, other)
  - d. How often patients are examined during Stelara (ustekinumab) therapy by a healthcare professional, and the type of professional (i.e., physician/prescriber, physician/non-prescriber, nurse, other)
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective actions to address non-compliance.
4. Report on the content, participation, and effectiveness of CME programs targeting prescribers and oncologists.
5. A summary of all reported serious infections and malignancies, with analysis of adverse event reporting by prescriber type (e.g., dermatologist, nurse, internist, oncologist).
6. Based on the information submitted, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

If you do not submit electronically, please send 5 copies of your proposed REMS as an amendment to your BLA. Prominently identify the amendment containing the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125261  
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold, capital letters at the top of the first page of the submission:

**BLA 125261  
PROPOSED REMS – AMENDMENT**

Application Type BLA  
Submission Number 125261  
Submission Code 00

Letter Date November 28, 2007  
Stamp Date November 29, 2007  
PDUFA Goal Date December 29, 2008

Reviewer Name Brenda Carr, M.D.  
Review Completion Date October 31, 2008

*Brenda Carr, MD 19 Nov 08  
Jill Lindstrom 19 Nov 08*

Established Name ustekinumab  
(Proposed) Trade Name Stelara  
Therapeutic Class IL-12/IL-23 antagonist  
Applicant Centocor

Priority Designation S

Formulation solution for subcutaneous administration  
Dosing Regimen Weeks 0, 4 then every 12 weeks  
Indication treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy  
Intended Population adult patients (18 years or older)

**Table of Contents**

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT</b>	<b>4</b>
1.1	Recommendation on Regulatory Action	4
1.2	Risk Benefit Assessment	4
1.3	Recommendations for Postmarketing Risk Management Activities	4
1.4	Recommendations for other Post Marketing Study Commitments	8
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND</b>	<b>9</b>
2.1	Product Information	9
2.2	Tables of Currently Available Treatments for Proposed Indications	9
2.3	Availability of Proposed Active Ingredient in the United States	10
2.4	Important Safety Issues With Consideration to Related Drugs	10
2.5	Summary of Presubmission Regulatory Activity Related to Submission	11
2.6	Other Relevant Background Information	14
<b>3</b>	<b>ETHICS AND GOOD CLINICAL PRACTICES</b>	<b>14</b>
3.1	Submission Quality and Integrity	14
3.2	Compliance with Good Clinical Practices	15
3.3	Financial Disclosures	15
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES</b>	<b>16</b>
4.1	Chemistry Manufacturing and Controls	16
4.2	Clinical Microbiology	17
4.3	Preclinical Pharmacology/Toxicology	17
4.4	Clinical Pharmacology	19
4.4.1	Mechanism of Action	20
4.4.2	Pharmacodynamics	20
4.4.3	Pharmacokinetics	20
<b>5</b>	<b>SOURCES OF CLINICAL DATA</b>	<b>21</b>
5.1	Tables of Clinical Studies	21
5.2	Review Strategy	25
5.3	Discussion of Individual Studies	26
<b>6</b>	<b>REVIEW OF EFFICACY</b>	<b>30</b>
6.1	Indication	30
6.1.1	Methods	30
6.1.2	Demographics	30
6.1.3	Patient Disposition	33
6.1.4	Analysis of Primary Endpoint(s)	33
6.1.5	Analysis of Secondary Endpoints(s)	34
6.1.6	Other Endpoints	35
6.1.7	Subpopulations	36
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	37
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects	43
6.1.10	Additional Efficacy Issues/Analyses	45
<b>7</b>	<b>REVIEW OF SAFETY</b>	<b>45</b>
7.1	Methods	45
7.1.1	Clinical Studies Used to Evaluate Safety	46
7.1.2	Adequacy of Data	46
7.1.3	Pooling Data Across Studies to Estimate and Compare Incidence	47
7.2	Adequacy of Safety Assessments	47
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	47

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

7.2.2	Explorations for Dose Response.....	55
7.2.3	Special Animal and/or In Vitro Testing.....	55
7.2.4	Routine Clinical Testing.....	55
7.2.5	Metabolic, Clearance, and Interaction Workup.....	56
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.....	56
7.3	Major Safety Results.....	56
7.3.1	Deaths.....	56
7.3.2	Nonfatal Serious Adverse Events.....	58
7.3.3	Dropouts and/or Discontinuations.....	79
7.3.4	Significant Adverse Events.....	81
7.3.5	Submission Specific Primary Safety Concerns.....	89
7.4	Supportive Safety Results.....	90
7.4.1	Common Adverse Events.....	90
7.4.2	Laboratory Findings.....	102
7.4.3	Vital Signs.....	109
7.4.4	Electrocardiograms (ECGs).....	110
7.4.5	Special Safety Studies.....	111
7.4.6	Immunogenicity.....	112
7.5	Other Safety Explorations.....	113
7.5.1	Dose Dependency for Adverse Events.....	113
7.5.2	Time Dependency for Adverse Events.....	114
7.5.3	Drug-Demographic Interactions.....	114
7.5.4	Drug-Disease Interactions.....	117
7.5.5	Drug-Drug Interactions.....	119
7.6	Additional Safety Explorations.....	119
7.6.1	Human Carcinogenicity.....	119
7.6.2	Human Reproduction and Pregnancy Data.....	119
7.6.3	Pediatrics and Effect on Growth.....	122
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	123
7.7	Additional Submissions.....	124
<b>8</b>	<b>POSTMARKETING EXPERIENCE.....</b>	<b>137</b>
<b>9</b>	<b>APPENDICES.....</b>	<b>140</b>
9.1	Literature Review/References.....	140
9.2	Labeling Recommendations.....	140
9.3	Advisory Committee Meeting.....	141

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

From a clinical perspective, it is recommended that a complete response action be taken on the application.

### 1.2 Risk Benefit Assessment

Ustekinumab is a first-in-class, fully human IgG1 $\kappa$  monoclonal antibody that binds to the p40 subunit of interleukin (IL)-12 and IL-23. The applicant proposes the product for treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. They propose a fixed weight-based dosing regimen under which patients  $\leq 100$  kg would be receive 45 mg at Weeks 0, 4, and every 12 weeks thereafter, and patients  $> 100$  kg would receive 90 mg on the same schedule.

The applicant conducted two adequate and well-controlled Phase 3 studies, in which primary efficacy was assessed at Week 12 by the proportion of subjects who achieved a 75% reduction in the Psoriasis Area Severity Index (PASI 75). A major secondary endpoint was the Physician's Global Assessment (PGA). The Phase 3 studies provided substantial evidence of efficacy of ustekinumab in the target population of patients with moderate to severe plaque psoriasis. In both studies, efficacy was demonstrated for both doses on the PASI and on the PGA. Efficacy outcomes were generally similar between dosing groups and across studies. Both doses were proven efficacious in both weight categories; however, higher efficacy outcomes were observed in heavier subjects ( $> 100$  kg) who received 90 mg of ustekinumab compared to those who received 45 mg. Efficacy was demonstrated in sub-groups.

The assessment of safety was based primarily on the integrated analyses of data from three studies (a Phase 2 study and the Phase 3 studies). In the reviewer's opinion, the applicant provided substantial evidence of the safety of ustekinumab in the target population through 18 months of exposure. Overall rates and patterns of serious adverse events suggested no increased risk when ustekinumab-treated subjects were compared to placebo-treated subjects or to each other (i.e., 45 mg compared to 90 mg). This conclusion held when specific categories of events were considered, including serious cardiac events, serious infections, serious malignancies, and serious nervous system disorders. Overall rates for treatment-emergent adverse events were generally similar between all treatment groups, and generally suggested no dose response when ustekinumab groups were compared (the most common adverse events were nasopharyngitis and upper respiratory tract infection). Adverse drug reactions were not worrisome in pattern or frequency of occurrence.

The safety database revealed no signals suggesting that patients with pharmacologic blockade of IL-12/IL-23 might manifest the vulnerabilities to the narrow spectrum of infections seen in individuals genetically deficient in these cytokines. Specifically, there were no reports of infections by nontuberculous mycobacteria or of salmonella. There was one report of a serious gastroenteritis, and the subject's presentation and clinical course did not suggest salmonellosis. Of note, 68 subjects with latent tuberculosis diagnosed during screening were enrolled in the trials (with appropriate treatment initiated either prior to or simultaneous with first administration

of study agent), and all were at some point exposed to ustekinumab because of the crossover design of the Phase 3 studies. Two additional subjects, were diagnosed with latent tuberculosis post-screening. Through the end of the reporting, there were no reports of complications from tuberculosis.

The safety database did not signal that the malignancy risk suggested in animal models might be translating to humans; however, a signal of this sort might not be revealed in a database in which the maximum duration of follow-up was through 18 months, with 373 ustekinumab-exposed subjects followed through this period. Similarly, the database might not be of sufficient size to detect low frequency events (infectious or malignant). Therefore, the available data permit only tentative conclusions regarding these risks, and additional, longer-term data are needed to assess for these theoretical risks in patients treated with ustekinumab.

Product labeling should advise of these potential risks (i.e. infections seen in those genetically deficient and malignancy signal in animal studies), but labeling should reflect that these risks are theoretical in nature, as they have not been evidenced in the database to date.

Benefit from treatment with ustekinumab in the target population has been adequately demonstrated. Safety through 18 months of exposure in the target population has been adequately demonstrated. Based on the available data, the reviewer has concluded that the benefits of treatment with ustekinumab appear to outweigh its risks. However, a Risk Evaluation and Mitigation Strategy (REMS) is required to ensure that the benefits of ustekinumab outweigh its risks. A REMS is necessary to manage the potential serious risks of infections and malignancies, and submission of an adequate REMS is recommended as a requirement for approval of this application. The REMS should include a Medication Guide and a communication plan.

The Medication Guide is necessary for patients' safe and effective use of ustekinumab. The communication plan should disseminate information about the REMS to encourage its implementation. It should target healthcare providers likely to be involved in the care of patients treated with ustekinumab, including those involved in management of the psoriasis and those involved in management of treatment-emergent illnesses (particularly those infectious or malignant in nature). The communication plan should provide information regarding screening procedures to ensure selection of patients appropriate for treatment with ustekinumab, advise of the particular infection susceptibilities of individuals genetically deficient in IL-12/IL-23 and advise of the malignancy signal reported with deficiency of IL-12/IL-23 in some animal studies. It should also advise of the uncertain and theoretical nature of the risks of particular infections and malignancy in patients treated with ustekinumab.

In the reviewer's opinion, healthcare providers are well aware of the broad categories of risk associated with any immunosuppressive therapy (malignancy, serious infections, opportunistic infections) and generally have a heightened sense of vigilance for these risks when such therapy is undertaken; however, it is important that providers be educated on particular, albeit theoretical, potential risks from use of ustekinumab and the reasons underlying the concerns from use of this product.

An Advisory Committee meeting was held on June 17, 2008, and committee members voted unanimously in favor of approval of ustekinumab. Following discussion largely framed around the malignancy issue, the Advisory Committee unanimously voted that subjects had been followed for an insufficient length of time and were nearly unanimous (10 of 11) in voting that the numbers of subjects studied were insufficient to characterize the risk(s) of ustekinumab. In the reviewer's opinion, the applicant has provided adequate evidence to support the safety and efficacy of their product for the indication proposed. However, while the reviewer favors

approval of the product, the reviewer cannot recommend approval in the absence of an adequate REMS to manage the potential serious risks of infections and malignancies.

#### Alternative Weight-Based Dosing Regimen

An alternative dosing regimen under which patients would be dosed according to three categories (rather than the two categories proposed by the applicant) was discussed at the Advisory Committee meeting. Under this regimen, patients  $\geq 70$  kg and  $< 100$  kg would receive 67.5 mg of ustekinumab (rather than 45 mg), with the intent of the intermediate dose being to maximize efficacy in this weight category. This approach was based on pharmacokinetic modeling, i.e. the intermediate dose has not been evaluated in clinical studies, and would more closely approximate mg/kg dosing than does the two-step regimen proposed by the applicant.

The reviewer recommends the two-step approach proposed by the applicant. In the reviewer's opinion, the projected outcomes for "mid-weight" patients administered 67.5 mg are not sufficiently higher than those demonstrated with dosing of 45 mg to recommend the increased exposure to ustekinumab to all subjects in this mid-weight category, when most are likely to achieve satisfactory outcomes with less exposure to ustekinumab. Additionally, the reviewer suspects that there will be patients who get results under the two-step regimen with which they are completely satisfied, but that fall short of PASI 75, a benchmark commonly employed in clinical studies, but, perhaps, less frequently in clinical practice.

The Advisory Committee voted 7 to 3 (one abstention) in favor of the two-step regimen.

#### Self-Administration

The applicant proposes that select patients have the option of self-administration of treatment. However, the only data submitted in support of self-administration reflected such being done under medical supervision at the investigative site. The applicant provided no data reflecting real-world use, i.e. self-administration outside of the supervised environment. Therefore, the applicant lacks adequate data to support self-administration.

The reviewer acknowledges that the technical complexities of subcutaneous injections are few. Self-injections are done daily by many patients with a variety of chronic diseases. However, the applicant's product is proposed for maintenance dosing every 12 weeks (i.e. every 3 months or 4 times per year). With such infrequency, it is unclear to what extent patients might become facile with procedures associated with self-injection of a liquid-in-vial product, and poor technique could have implications for both safety and efficacy outcomes. Presentation for re-treatment would ensure some measure of follow-up and allow for evaluation for conditions that might preclude re-treatment.

This is a first-in-class product about which much is still to be learned. The reviewer does not recommend release of the product into the marketplace with self-administration as an option at launch. The reviewer considers it reasonable to reconsider self-administration once more safety data are available and were the applicant to provide adequate information to support this proposal (including data reflecting unsupervised, real-world use and methods for educating on proper procedures).

The Advisory Committee voted 7 to 4 against self-administration.

### **1.3 Recommendations for Postmarketing Risk Management Activities**

The following postmarketing risk management activities are recommended as being required.

The applicant should implement and/or adhere to their proposed plans for pharmacovigilance activities as below:

1. PSoriasis Longitudinal Assessment and Registry

The PSoriasis Longitudinal Assessment and Registry (PSOLAR; study C0168Z03) is ongoing for infliximab, and patients treated with ustekinumab should be added when appropriate. It is based in North America and designed to collect data on psoriasis patients eligible to receive systemic therapies, including generalized phototherapy and biologics. It is intended to track adverse events in approximately 8,000 patients, and the applicant projects that 4,000 of these patients will have been exposed to ustekinumab.

The registry will actively collect all serious adverse events and other targeted adverse events (malignancies, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, congestive heart failure, hepatotoxicity, and hematologic events). The registry should also include diverticulitis as a targeted adverse event. The registry will also collect data on disease activity and on pregnancy outcomes. The applicant anticipates that the registry will last 8 years from the enrollment of the last subject.

The applicant should submit a revised protocol reflecting the intent to enroll patients treated with ustekinumab.

2. Nordic Database Initiative

The Nordic Database Initiative (NDI) is a proposed prospective, 5+year extendable study of adverse events in all psoriasis patients in Sweden treated with ustekinumab in actual clinical practice. Per the applicant, Sweden has several healthcare databases that together capture information on all persons living there. The applicant intends to combine the data from these registers into one analytical data set, and the applicant states this will capture all psoriasis patients in Sweden and provide the denominator for comparison of adverse events of interest. Per the applicant, the data set would allow for several comparisons, including by disease and indication and with or without ustekinumab exposure. They ultimately expect to follow approximately 4,000 ustekinumab patients for at least 10 years; however, the number of patients in the data set will be a function of both the number of moderate to severe psoriasis patients in Sweden and the uptake of ustekinumab.

These large databases can potentially capture more rare adverse events than might be captured in targeted (e.g. disease-specific registry) initiatives. Furthermore, they offer the ability to perform analyses free of several sources of enrollment bias. The applicant will query these data sets for adverse events of special interest, such as malignancies, infections, cardiovascular events, and deaths over the entire national populations that can include Sweden and other northern European countries. These analyses will be compared where relevant with outcomes from a disease/agent-specific registry based in North America.

A protocol has not yet been finalized, but should be submitted to the Agency once available. The product has not been approved in the European Union.

3. Pregnancy Research Initiative (study C0168T71)

This initiative is ongoing in Sweden and Denmark for infliximab and patients treated with ustekinumab exposure should be added when appropriate. It is a prospective, 5-year observational study of pregnancy outcomes in pregnant women with exposure to ustekinumab in actual clinical practice, and of the health status of their infants during a one-year follow-up period. This will be a current exposure-based cohort study in which women with diseases of interest but without prenatal ustekinumab exposure, and their infants, will serve as controls.

The applicant should submit a revised protocol reflecting the intent to enroll patients treated with ustekinumab.

4. The applicant should establish a U.S.-based prospective, observational pregnancy exposure registry that compares the pregnancy and fetal outcomes of women exposed to ustekinumab during pregnancy to an unexposed control population. Outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life.
5. The applicant should conduct a lactation study in women who are breastfeeding while exposed to ustekinumab. This study may be conducted in a subset of women enrolled in the U.S.-based pregnancy registry, who choose to breastfeed their infants and is intended to assess for the presence of ustekinumab in breast milk and potential effects in nursing infants.

#### **1.4 Recommendations for other Post Marketing Study Commitments**

The following are recommendations for Post Marketing Study Commitments:

1. It is recommended that the safety and efficacy of long-term continuous use of ustekinumab be evaluated as proposed with the long-term extension of the Phase 3 psoriasis trials through 5 years from initial administration of product (264 weeks).
2. It is recommended that the applicant further evaluate maintenance dosing (less frequent dosing, lower doses).
3. It is recommended that the applicant conduct an in vitro study or studies to determine whether IL-12 and/or IL-23 modulate CYP enzyme expression and whether ustekinumab is able to reverse the effects of IL-12/IL-23 on CYP expression (e.g., in vitro hepatocyte study). An alternative in vivo approach would be to determine the potential of ustekinumab for the alteration of CYP substrate metabolism in psoriasis patients (e.g., a cocktail study with CYP probe drugs).
4. It is recommended that the applicant develop an assay with which the presence of ustekinumab does not interfere.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Ustekinumab (“CNTO 1275”) is a first-in-class, fully human IgG1 $\kappa$  monoclonal antibody that binds to the p40 subunit of interleukin (IL)-12 and IL-23. IL-12 and IL-23 have been implicated in the pathogenesis of psoriasis. They are heterodimer cytokines and share the IL-12p40 subunit as below<sup>1</sup>:

- IL-12p40 + IL-12p35 = IL-12
- IL-12p40 + IL-23p19 = IL-23

IL-12 and IL-23 also share the immune cell transmembrane receptor subunit IL-12 receptor beta-1 (IL-12R $\beta$ 1). The applicant describes that their product “neutralizes (IL-12 and IL-23) bioactivity by preventing these cytokines from binding to their IL-12R $\beta$ 1 (IL-12 receptor beta-1) receptor protein expressed on the surface of immune cells.”

T cells are fundamental to the induction and maintenance of psoriatic plaques.<sup>2</sup> IL-12 is produced by dendritic cells and macrophages and induces differentiation of CD4 naïve T cells to T-helper 1 (Th1) cells and activates natural killer cells, both of which produce interferon (IFN)- $\gamma$  which plays an important pathogenic role in psoriasis by “facilitating” the infiltration of T-cells into the epidermis and inducing keratinocyte proliferation. IL-23 plays an important role in stimulating CD4+ T cells to produce IL-17 which has critical roles in autoimmune inflammation and synergizes with IFN- $\gamma$  to increase the production of pro-inflammatory cytokines by keratinocytes.<sup>1</sup>

### 2.2 Tables of Currently Available Treatments for Proposed Indications

The applicant proposes their product for “treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.” In the studies relied on to support the marketing application, disease of this severity was defined as a Psoriasis Area and Severity Index (PASI) score of  $\geq 12$  and Body Surface Area (BSA) involvement of  $\geq 10\%$ .

In practice, a recommendation of phototherapy or systemic therapy is based on clinical judgment, and the decision to proceed is one made between patient and physician with careful attention to risk-benefit considerations, since all of the therapies carry significant risk. Some clinicians may employ a BSA involvement of  $\geq 10\%$  as a criterion for when a patient with psoriasis might become a candidate for phototherapy or systemic therapy (disease involving the palms and/or soles can be debilitating and considered severe despite involving an area of  $< 10\%$ ). Disease of this severity may be challenging to adequately manage solely with topical therapies, and products which might be considered therapeutic options for the applicant’s target population are presented in the table below.

*Comment: The review will not address topical therapies, as disease that is entirely amenable to treatment with topicals is not the severity of disease for which the applicant’s product is intended. Details of the PASI are in Appendix 9.5. It is unclear to what extent clinicians employ*

*the PASI to make a determination that alternatives to topical therapies should be considered to manage the disease.*

Product	Class	Warnings/Precautions*
Acitretin	retinoid	teratogen ; hepatotoxicity ;hyperostosis ;lipid effects
Methotrexate	folate antagonist	liver fibrosis/cirrhosis ; hematologic toxicity;teratogen
Cyclosporine	inhibits IL-2	hypertension ; nephrotoxicity; serious infections; malignancy
Alefacept	inhibits LFA-3/CD2 interaction.	lymphopenia ; serious infections ; ;malignancies
Efalizumab	bindsCD 11a (I)	serious infections ;malignancies ; immune-mediated thrombocytopenia and hemolytic anemia
Etanercept	TNF-blocker	serious infections (including TB) ; central nervous system demyelinating disorders;hematologic events (pancytopenia);malignancies reactivation of hepatitis B
Adalimumab	TNF blocker	serious infections (including TB), malignancies; reactivation of hepatitis B; demyelinating disease ; hematologic reactions (pancytopenia)
Infliximab	TNF blocker	serious infections (including TB) ; hepatosplenic t-cell lymphomas

\*These are not intended as comprehensive lists

### Phototherapy

This therapy entails exposures to UVB (including narrowband) or to UVA in combination with the photosensitizer, Psoralen, a photochemotherapy that goes by the acronym PUVA. The risk of squamous cell carcinoma (of the skin) is increased with cumulative high-dose exposure to PUVA.<sup>3</sup> Phototherapy requires frequent office visits (e.g. three times per week), and may be challenging for some patients' schedules to accommodate.

### **2.3 Availability of Proposed Active Ingredient in the United States**

The product is not available in the United States (it is not marketed anywhere).

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Ustekinumab is first in its class. However, it is an immunosuppressant and risks attached to immunosuppressive therapy in general include serious infections, opportunistic infections and malignancy. However, there may be particular risks attached to ustekinumab because of its mechanism of action.

Kindreds of individuals with mutations in genes involved in aspects of the IL-12/IL-23 dependent IFN $\gamma$  pathway (making for IL-12/IL-23 deficiency) have been identified.<sup>4,5,6</sup> Affected individuals demonstrate particular susceptibilities to infections from poorly pathogenic environmental mycobacteria (i.e. non-tuberculous), bacillus Calmette-Guerin (BCG) vaccines (dissemination), and nontyphoidal salmonella species.<sup>4,5,6,7,8,9</sup> They may also be more vulnerable to infection by *M. tuberculosis*.<sup>7</sup>

To date, vulnerabilities to infection appear to be limited to this narrow spectrum of intracellular bacteria<sup>4,6,7</sup>, and they are otherwise described as healthy and without other overt manifestations of immunosuppression.<sup>8,9</sup> The reviewer found no reports of any malignancy signal in these individuals; however, most reports appear to be of events in children and therefore may not reflect longer term outcomes.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The psoriasis program was conducted under IND 9590. Key pre-submission regulatory activities included the following:

- Pre-IND teleconference (November 28, 2000)
- End-of-Phase 2 (EOP2)/Pre-Phase 3 meeting (May 26, 2005)
- Pre-BLA teleconference (March 14, 2007)

*Comment: The pre-IND teleconference and the EOP2/Pre-Phase 3 meeting occurred while the IND was in the Center for Biologics Evaluation and Research (CBER), i.e. prior to the IND being transferred to the Division of Dermatology and Dental Products (DDDP).*

### Pre-IND teleconference: November 28, 2000

Discussion included:

- the general strategy for manufacturing and additional CMC informational needs
- the proposed toxicology program and additional informational needs
- a proposed Phase 1 study

### End-of-Phase 2/Pre-Phase 3 meeting: May 26, 2005

The applicant was provided with comments about their development program and the draft Phase 3 protocols submitted in the briefing package. Comments and discussion included:

1. The safety and efficacy of continuous and/or intermittent long-term use (e.g. one year) should be studied. Additionally, the applicant should evaluate duration of response, ability to recapture response upon re-treatment and rebound.
2. Test various doses and find the one with a favorable risk:benefit profile.
3. PASI  $\geq 75$  would be a meaningful treatment response, as would clear or minimal disease on an appropriate static Physician Global Assessment (PGA). PASI  $> 50$  but  $< 75$  cannot be considered a satisfactory response.
4. Subjects who do not adequately respond (PASI  $< 75$ ) should be considered for withdrawal from therapy or assignment to a different treatment regimen, depending on their outcome (e.g., different plans for those PASI  $\geq 50$ , but  $< 75$  vs PASI  $< 50$ ).
5. The applicant proposed to evaluate new induction regimens in the Phase 3 studies than were evaluated in Phase 2. A well-designed Phase 2 study conducted in subjects with moderate to severe plaque psoriasis would allow for better design of the Phase 3 study to further optimize the dose.
6. Regarding the applicant's plans to evaluate fixed, weight-based dosing, the Agency expressed concern about subjects "at either end of the spectrum for weight treated." This approach could result in insufficient numbers of subjects at the either extreme of the weight spectrum to "exclude important differences in either efficacy or safety." The applicant was advised, "to have, by the time of submission of a BLA, adequate information to assess this question and ensure that the risk:benefit comparison for patients at both extremes of weight remains favorable."
7. The applicant was advised to consider a randomized withdrawal methodology to assess maintenance therapy, e.g. re-randomizing subjects to either placebo or continued treatment at 9 months and then re-evaluating at 1 year.



18. The applicant sought and received agreement that a “positive treatment effect, and measure by the static PGA scoring system, could also be used in labeling or promotional materials.
19. The Agency commented that some safety data may be obtained from the Phase 2 study, which would ultimately need to be combined with the Phase 3 study.
20. The Agency informed the applicant that because psoriasis is a chronic disease, evaluation of the safety and efficacy of the primary treatment regimen is critical, and evidence of sustained efficacy would be required for up to one year, e.g. conduct an open-label phase in which responders undergo randomized withdrawal at 9 or 10 months, depending on the dosing regimen, but the endpoint would be measured at one year and compared with the placebo group.

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

b(4)

23. The applicant sought agreement that the proposed plans for self-administration during the Phase 3 clinical studies would be appropriate to support approval of ustekinumab for self-administration; the Agency did not agree.
24. The applicant stated that they intended to have their product approved as a single use subcutaneous self-administered product using an auto-injector. The Agency advised that to market the auto-injector device, the applicant would be required to:
  - Establish efficacy and safety of ustekinumab in pre-filled syringes in the Phase 3 trials.
  - Provide functional and mechanical testing data of the auto-injector and package support of the combination product (biologic/device).
  - Demonstrate bioequivalence between the to-be-marketed ustekinumab in an auto-injector and ustekinumab liquid in the pre-filled syringe used in the Phase 3 trials.
25. The Agency agreed with a deferment of a pediatric study until after approval for use in adults and if the risk:benefit profile supports initial studies in children.
26. The applicant was advised that the IND was going to be transferred to the Division of Dermatology and Dental Drug Products (DDDDP; now Division of Dermatology and Dental Products).

b(4)

*Comment: The applicant revised the protocols for the Phase 3 studies based on Agency comments' advice pertaining to the draft Phase 3 protocols submitted in the briefing package for the EOP2/pre-Phase 3 meeting. The applicant did not submit the revised protocols for Agency review and comment prior to undertaking the Phase 3 trials.*

Pre-BLA Clinical Teleconference with the Division of Dermatologic and Dental Products  
(March 14, 2007)

Comments and discussion included:

1. Although the subgroups may be small, the applicant should provide analyses by weight for the individual studies as well as for the pooled data.
3. It was acceptable to pool the safety data from the Phase 2 and 3 studies without including the Phase 1 studies.
4. Regarding self administration, the Agency's concern was whether safety and efficacy are the same when the product is self-administered versus administered by a health care professional. The Agency stated, "we are not optimistic that the sponsor has enough data to support a self administration claim but (the applicant) should provide the data they have from the clinical trial."

b(4)

## 2.6 Other Relevant Background Information

Other relevant background information has been incorporated into other sections of this review.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

Division of Scientific Investigations (DSI) inspections were requested for three Phase 3 study sites, selected because they had some of the largest enrollments, and greatest treatment effects. The DSI also investigated the applicant's monitoring practices for the Phase 3 studies.

Following selection of these sites, the statistical reviewer, Kathleen Fritsch, Ph.D., discovered that the principal investigators at these sites were among several who participated in both Phase 3 studies, i.e. several investigators enrolled into both Phase 3 studies, C0743T08 (T08) and C0743T09 (T09). The sites selected for inspection were:

Investigator	Study site; Number enrolled in T08	Study site; Number enrolled in T09
Howard Sofen, MD Los Angeles, CA	031; 42 subjects	124; 60 subjects
Craig Leonardi, MD St. Louis, MO	016; 37 subjects	118; 44 subjects
Robert Matheson, MD Portland, OR	021; 42 subjects	119; 50 subjects

*Comment: Dr. Fritsch conducted analyses which excluded subjects who were enrolled by investigators who participated in both studies, and efficacy outcomes for both dosing groups (45 and 90 mg) and results in both studies remained highly statistically significant ( $p < 0.001$ ). From the statistical review, "(w)ith the large number of centers and relatively small sample sizes, the impact of any individual center on the efficacy results is limited." The clinical reviewer agrees.*

*The reader is referred to the statistical review for additional details and discussion of these analyses.*

DSI inspectors concluded that Drs. Sofen and Leonardi “did not ensure that the investigation was conducted according to the investigational plan” (from Clinical Inspection Summary). Specifically, each investigator dispensed different kits than were identified by the interactive voice response system (3 subjects each). However, the DSI concluded that the data generated by all sites inspected and the monitoring practices of the applicant appeared “acceptable in support of the pending application.

### 3.2 Compliance with Good Clinical Practices

The applicant attested that all studies in the psoriasis development program were conducted in accordance with ICH GCP (statement found in each of the study reports for the five studies submitted in support of this application).

### 3.3 Financial Disclosures

Financial disclosure forms were submitted for five investigators (all from the Phase 3 studies T09):

- \_\_\_\_\_ disclosed receipt of a fellowship grant in excess of \$25, 000 funding research in psoriasis outcomes for one year.
- \_\_\_\_\_ disclosed a one-year fellowship grant in excess of \$25, 000 provided to the principle investigator for research on psoriasis outcomes.
- \_\_\_\_\_ disclosed that the principle investigator was receiving funding in excess of \$25, 000 for a one-year fellowship trainee.
- \_\_\_\_\_ disclosed receipt of funding for one-year psoriasis research fellowship amounting to \$50,000.
- \_\_\_\_\_ disclosed receipt of \$104,838 from the applicant from January 1, 2002 through July 7, 2007: \$79,838 in consultation and honorarium fees and \$25,000 support for clinical research fellow (July 1, 2006 to June 30, 2007).

*Comment: Site \_\_\_\_\_ randomized one subject to each treatment group; none were PASI 75 responders. Site \_\_\_\_\_ randomized 17 subjects: PASI 75 responders were: placebo 0.0% (0/13), 45 mg 33.3% (2/6), and 90 mg 50% (3/6). In the reviewer’s opinion, the impact on overall efficacy outcomes from these 2 centers is minimal because of the small numbers of subjects involved (as well as their outcomes) and the large number of centers.*

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The following is summary information from the Quality Review by Laurie Graham, M.S. and the Quality Review Team Leader Summary by Barbara Rellahan, M.S., Ph.D. The reader is referred to those documents for additional details and information.

#### Cell Bank

Inspection of the St. Louis facility revealed failure of the working cell bank (WCB) 1 to meet acceptance criteria for viability at thaw on several attempts and for reasons undetermined. This represented a very significant finding as this site was used to manufacture process consistency lots. WCB1 was removed from production and replaced by WCB 2 for production activities. (The applicant submitted stability data that supported the use of WCB2 in the commercial manufacturing process.)

During the review process and following extensive discussion with the Agency pertaining to the stability of working cell banks, the applicant submitted additional stability data for WCB 1 (acquired from their continued investigation into this matter). The new data suggested that, "the viability of the cell bank is not substantially different from what it was when the cell bank was initially used in production and supports its use for (ustekinumab) commercial production" (Quality Team Leader summary).

#### Assay

Per the Quality Review (Section 5.3.1.4), the applicant's immunogenicity assay has been adequately validated. The sensitivity of the assay to detect antibody responses to ustekinumab was evaluated, and the assay detection limit is 24 ng/mL. Specificity was demonstrated. However, the presence of ustekinumab in the serum interferes with the assay: "At 1 ng/mL Ustekinumab was shown to reduce the human (anti-drug antibody) response by 73%."

Per the Quality Review, the validation of the assay to detect neutralizing antibodies was "acceptable." The presence of ustekinumab in the serum should not interfere with this assay as it is only performed once antibody-positivity has been established.

**Comment:** Per the Clinical Pharmacology review by Abimbola Adebawale, Ph.D., "The mean (SD) steady-state trough serum concentrations at Week 28 in study C0743T08 and C0743T09 was 0.33 (0.74) µg/mL and 0.31 (0.33) µg/mL, respectively (45 mg every 12 weeks), and 0.059 (0.60) µg/mL and 0.64 (0.64) µg/mL respectively, (90 mg every 12 weeks)." Thus, in the Phase 3 studies, the mean steady state levels of ustekinumab for both proposed dosing regimens were higher than the serum level at which its presence would interfere with the immunogenicity assay. The in vitro results discussed in the Quality Review were substantiated by the results of immunogenicity testing from the clinical studies (see Section 7.4.6).

#### Additional Information

Ustekinumab is not thought likely to induce antibody dependent cellular cytotoxicity or complement dependent cellular cytotoxicity, as it cannot bind IL12 or IL-23 that is already bound to the cell surface receptors IL-12  $\beta$ 1.

The product is photosensitive (it degrades). It is packaged in an opaque paperboard carton and should be stored in this carton under refrigeration at 2-8°. It should not be shaken or frozen. It is provided as a sterile solution in single-use, 2-mL glass vials which contain either 45 mg/0.5mL or 90 mg/1.0 mL. The product does not contain preservatives; therefore, unused portions should be discarded.

#### **4.2 Clinical Microbiology**

The product is not an antimicrobial.

#### **4.3 Preclinical Pharmacology/Toxicology**

The pharmacology/toxicology review was performed by Jiaqin Yao, M.D., Ph.D.

#### General Toxicity

Dr. Yao discusses three general toxicity studies, each of which included evaluation of potential effects of ustekinumab on the cardiovascular and respiratory systems [electrocardiograms (ECGs), blood pressures, heart rates, and respiratory rates] and the central nervous system (clinical observations, rectal body temperature). Select findings from these studies are described in brief below, and the reader is referred to Dr. Yao's review for more comprehensive information.

A study in which cynomolgus monkeys were dosed up to 45 mg/kg weekly for 4 weeks revealed "no treatment-related effects on mortality, clinical observations, body weights, food consumption, physical examinations (heart rate, respiratory rate, capillary refill time, and body temperature), cardiovascular parameters (ECG, heart rate, and blood pressure), macroscopic findings, or organ weights."

A second study, in which cynomolgus monkeys were dosed up to up to 45 mg/kg weekly for 4 weeks, appears to have included more comprehensive testing. Dr. Yao reports that this study revealed "no treatment-related effects on mortality, clinical signs, body weight, food consumption, body temperature, indirect blood pressure, electrocardiograms, physical and ophthalmic evaluations, coagulation, serum chemistry, organ weight, and macroscopic or histopathologic evaluations."

Dr. Yao lists key findings from a 26-week subcutaneous dose (22.5 or 45 mg/kg) toxicity and toxicokinetic study conducted in cynomolgus monkeys as including no treatment-related effects on survival, clinical signs, blood pressure, electrocardiograms, clinical pathology, histopathological examinations, or functional immune responses. Additionally, there were no treatment-related differences in histomorphology or immunostaining (CD3 and CD20) of lymphoid organs. No delayed signs of toxicity were observed in the 12-week recovery period. However, one (of 10) monkeys showed signs of bacterial enteritis.

***Comment:*** Per Dr. Yao's review, based on mg/kg dosing, the 45 mg/kg dosing evaluated in the studies above is 45 times the highest dose intended for clinical use (in psoriasis patients).

Dr. Yao's summary statement regarding the general toxicity studies was, "No significant adverse effects were noted in these studies, except that in the 26-week subcutaneous study, one out of 10 monkeys administered 45 mg/kg CNTO 1275 for 26 weeks exhibited signs of bacterial enteritis."

### Carcinogenicity

There is information in the literature from animal models suggesting a role for IL-12 in tumor surveillance and that its inhibition may result in a heightened risk for malignancy. Dr. Yao's review includes discussion of some of these animal data including:

- Murine IL-12 had an anti-tumor effect in mice, associated with enhanced anti-tumor activities of T cells and NK cells, induction of IFN- $\gamma$  production and other cytokines induced-by IL.
- Murine IL-12 reduced experimental pulmonary metastases of melanoma cells in mice and inhibited subcutaneous growth of established melanoma, reticular, and renal cell carcinomas, and increased survival time of tumor bearing mice.
- Murine IL-12 delayed tumor appearance and reduced tumor incidence in a mouse tumor promotion model.
- IL-12/IL-23p40 knockout (KO) mice developed UV-induced tumors earlier and more frequently than did wild-type mice, and tumors generated in IL-12/IL-23p40 KO mice grew faster and had greater invasion potential.

***Comment:*** As previously discussed, the risk of squamous cell carcinoma (SCC) increases with cumulative exposure to high-dose PUVA (and melanoma). It is theoretically possible that the risks might be further increased in patients treated with ustekinumab who have had previous high-dose PUVA treatment. However, all discussion of human carcinogenicity risk based on the animal data is entirely theoretical. The reader is referred to Dr. Yao's review for additional details and information regarding the animal data..

Nonclinical carcinogenicity studies were not conducted with ustekinumab. A traditional two-year rodent carcinogenicity study cannot be done with the product because it does not bind rodent IL-12. It is species-specific in binding to human and non-human primate IL-12.

In a facsimile sent June 15, 2006, the Agency informed the applicant that a "6-month monkey study conducted to date did not provide treatment durations that cover(ed) a sufficiently long duration of the monkey life span to be considered definitive for carcinogenicity...(t)he Division understands that it may not be informative to conduct a study in a normal rodent with (ustekinumab) since this antibody does not bind to rodent IL-12. Other animal models that could be developed include a transgenic rodent model expressing human IL-12 or use of a rodent specific antibody to IL-12. With such a model, life time studies in the rodent could be conducted to help ascertain how significant the risk of increased malignancy may be."

**Comment:** *Although the monkey study was determined to be inadequate for assessment of carcinogenicity for the reasons stated above, results from this study included (from Dr. Yao's, review), "No tumors or histopathological evidence of pre-neoplastic changes...in organs or tissues examined" (the monkeys were dosed subcutaneously at dose levels up to 45 mg/kg twice weekly for 6 months with a 3-month post-dose observation period).*

In response to the Agency's comments, on February 23, 2007 the applicant submitted a protocol proposing evaluation of tumor immune surveillance in a mouse syngeneic tumor model (mouse anti-IL-12 mAb would be measured). The Agency reviewed the applicant's proposed plans for the mouse study, and at the Pre-BLA teleconference (March 14, 2007) advised the applicant that although concerns persisted regarding the "tumorigenic potential" of ustekinumab and "unquantitated increased risk of tumor formation":

"After extensive consideration, we do not believe that the proposed study...in mice will provide definitive data to permit risk assessment. We believe that a negative finding in this study would not ameliorate the concern about the possible increased risk of malignancy in humans with long term use of (ustekinumab). Because of the limited utility of such a study and the existing database for IL-12 effects, we do not believe that such a study is required for a BLA."

At the Pre-BLA teleconference, the Agency recommended that the BLA include "a thorough discussion of the nonclinical data you have collected and the literature and outline your risk management plan for the potential increase in malignancies that may occur with (ustekinumab). Additionally, the Agency advised the applicant that "labeling ...will likely need to have strong warnings about the risk of malignancy."

**Comment:** *The applicant's proposed Risk Management Plan is discussed in Sections 7.7 and 8.*

#### Immunotoxicity

These evaluations were incorporated into the general and developmental toxicity studies. Ustekinumab was not associated with immunotoxicity or immunosuppression in monkeys. "(Ustekinumab) did not cause toxicologically significant effects on functional immune response to a neoantigen or delayed type hypersensitivity responses, did not deplete or otherwise alter lymphocyte subpopulations, and did not reduce ex vivo lymphoproliferative responses to T-cell mitogens. There were no (ustekinumab)-related macroscopic observations or adverse effects on organ weights at necropsy, no (ustekinumab)-related histopathology findings observed in lymphoid tissues of juvenile, young adult or adult monkeys, and no altered distribution of T and B-lymphocytes in lymphoid tissue."

#### Reproductive and Developmental Toxicity

The applicant conducted the following studies in cynomolgus monkeys dosed up to 45 mg/kg of ustekinumab (subcutaneous or intravenous administration):

- a male fertility study,
- two embryo-fetal development toxicity studies, and

- an embryo-fetal development and pre- and postnatal development toxicity study have been conducted. A female fertility study was conducted in mice using an analogous IL-12/IL-23 p40 antibody.

Dr. Yao reported that no significant adverse effects were noted in any of these studies.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

The applicant's description of the mechanism of action was presented in Section 2.1 of this review, and the mechanism of action has been demonstrated. Per Section 3.2.S.1.3 of the Quality Review by Laurie Graham, M.S:

"The ability of Ustekinumab to bind with high affinity to IL-12 and IL-23 was determined by Biacore analysis... Ustekinumab has been shown to inhibit the binding of IL-12 and IL-23 to the IL-12  $\beta$  1 receptor chain... Ustekinumab has also been shown to inhibit the binding of IL-12 and IL-23 to cell lines which express endogenous dual receptor chains. In vitro Ustekinumab has been shown to inhibit human IL-12 and IL-23 induced signaling in human primary cells, human cell lines, and mouse splenocytes... This includes an inhibition of IL-12 induced interferon gamma (IFN- $\gamma$ ) secretion from an NK cell line, NK92MI, which is used as the potency assay for Ustekinumab."

### 4.4.2 Pharmacodynamics

The applicant conducted exploratory histological analyses on specimens obtained from psoriatic lesions in the Phase 2 study C0379T04. Per the Clinical Pharmacology review by Abimbola Adebowale, Ph.D., the results support the hypothesis that ustekinumab decreases the inflammatory infiltrate and epidermal hyperplasia in psoriatic lesions.

Ustekinumab had no apparent effects on serum concentrations of chemokine/cytokines hypothesized to be associated with psoriasis. Additionally, the product had no apparent effect on the major T lymphocyte populations reflective of immune status.

***Comment:*** *The reader is referred to the Dr. Adebowale's review for additional details and information on these investigations.*

### 4.4.3 Pharmacokinetics

An overview of the pharmacokinetics is presented below excerpted from Dr. Adebowale's (the reader is referred to her review for addition details of these processes):

#### Absorption:

"In healthy subjects...the median Tmax occurred approximately 8.5 days after a single 90 mg SC administration. This was comparable to the median Tmax of 7 to 14 days obtained in subjects

with psoriasis (...approximate dose ranging from 24 to 240 mg and...dose = 45 mg and 90 mg) following a single SC administration of ustekinumab.

“Distribution:

“The mean (SD) values of the apparent volume of distribution ( $V_z/F$ ) following a single SC administration were 72.8 (34.2) to 178.7 (85.2) mL/kg in psoriasis subjects (C0379T02; dose = 24 to 240 mg and, C0379T04; dose = 45 mg and 90 mg) and 90.2 (33.1) mL/kg in healthy subjects (C0743T11) following a single 90 mg dose.

“Metabolism:

The exact metabolic pathway for ustekinumab has not been characterized. The applicant stated that no studies on metabolites of ustekinumab have been performed and are not expected for monoclonal antibodies (ICH S6). Metabolism of ustekinumab is expected to be in the same manner as other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways).

“Elimination

In psoriasis subjects, the mean (SD) terminal half-life after a single SC administration (C0379T02; dose = 24 to 240 mg and, C0379T04, dose = 45 mg and 90 mg) was from 14.9 (4.6) to 45.6 (80.2) days. The mean (SD)  $t_{1/2}$  after multiple SC administrations (C0379T04) of 45 mg and 90 mg was 24.9 (7.9) days and 28.1 (7.3) days, respectively.”

*Comment: The relationship between pharmacokinetics, weight and PASI outcomes is discussed in Section 6.1.8.*

## 5 Sources of Clinical Data

### 5.1 Tables of Clinical Studies

The applicant conducted five clinical studies in the development program for psoriasis:

- two Phase 1 studies: C0379T01 and C0379T02
- one Phase 2 study: C0379T04
- two Phase 3 studies: C0743T08 and C0743T09

Table of these clinical studies follow [Source: Appendix A.1 from the Integrated Summary of Safety (ISS)].

Appendix A.1 Description of Clinical Efficacy and Safety Studies									
Study ID	No. of Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal Study Status	Design & Control Type	Study & Control Drugs Dose, Route, & Regimen(s)	Study Objective(s)	No. of Subjects by Arm Entered/ Completed	Duration of Treatment	Sex Median Age (Range)	Diagnosis Inclusion Criteria
<b>PSORIASIS STUDIES</b>									
<b>Phase I Studies</b>									
C0379T01	2 centers US	06 Apr 2001 Completed 16 Aug 2002 18 subjects enrolled/ 23 planned Completed	Phase I, multicenter, open-label, dose-ascending, nonrandomized, first-in-human trial with single IV administrations of CNTO 1275.	Subjects received a single dose of CNTO 1275 by IV infusion. Cohort 1: 0.09 mg/kg IV Cohort 2: 0.37 mg/kg IV Cohort 3: 0.9 mg/kg IV Cohort 4: 4.5 mg/kg IV	<b>Primary:</b> To establish short-term safety, tolerability, and PK profiles of single, ascending, IV administrations of CNTO 1275 in subjects with moderate to severe psoriasis vulgaris. <b>Secondary:</b> To assess the immunogenicity, PD, and clinical response to single, ascending, IV administrations of CNTO 1275 in subjects with moderate to severe psoriasis vulgaris.	Cohort 1: 4/4 Cohort 2: 4/4 Cohort 3: 5/5 Cohort 4: 5/5	Single 2-hour infusion with follow-up through Week 16.	M: 14 F: 4 43.5 yrs (23-55 yrs)	Psoriasis vulgaris Men and women, ages 18 to 65, with moderate to severe plaque psoriasis vulgaris involving $\geq 3\%$ BSA and who, in the opinion of the investigator, were in general good health.

Appendix A.1 Description of Clinical Efficacy and Safety Studies									
Study ID	No. of Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal Study Status	Design & Control Type	Study & Control Drugs Dose, Route, & Regimen(s)	Study Objective(s)	No. of Subjects by Arm Entered/ Completed	Duration of Treatment	Sex Median Age (Range)	Diagnosis Inclusion Criteria
C0379T02	3 centers US	25 Jun 2003 Completed 28 May 2003 21 subjects enrolled/ 20 planned Completed	Phase I, multicenter, randomized, double-blind, placebo-controlled, sequential dose escalation study with single SC administrations of CNTO 1275.	Single dose, SC injection within dosing cohorts. Group I: Dosing Cohort 1: 0.27 mg/kg SC CNTO 1275 or SC placebo Dosing Cohort 2: 0.675 mg/kg SC CNTO 1275 or SC placebo Group II: Dosing Cohort 1: 1.35 mg/kg SC CNTO 1275 or SC placebo Dosing Cohort 2: 2.7 mg/kg SC CNTO 1275 or SC placebo	<b>Primary:</b> To assess the safety and PK of single SC administrations of CNTO 1275 in subjects with psoriasis vulgaris. <b>Secondary:</b> To assess the immunogenicity, PD, and clinical response of single SC administrations of CNTO 1275 in subjects with psoriasis vulgaris.	Group I: Cohort 1: 5/5 Cohort 2: 4/4 Group II: Cohort 1: 4/4 Cohort 2: 4/4 Placebo: 4/4	Single SC injection with follow-up through Week 24.	M: 15 F: 6 49 yrs (26-69 yrs)	Plaque psoriasis Men or women, ages 18 to 65, with moderate to severe plaque psoriasis involving $\geq 3\%$ BSA and who, in the opinion of the investigator, were generally in good health.

Best Possible Copy

Appendix A.1 Description of Clinical Efficacy and Safety Studies

Study ID	No. of Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal Study Status	Design & Control Type	Study & Control Drugs Dose, Route, & Regimen(s)	Study Objective(s)	No. of Subjects by Arm Entered/ Completed	Duration of Treatment	Sex Median Age (Range)	Diagnosis Inclusion Criteria
Phase 2 and 3 Studies									
C0379704	46 centers 28 US 12 Canada 4 Germany 3 Belgium	25 Jun 2003 Completed 09 Mar 2005 320 subjects enrolled/ 300 planned Completed	Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel study of single and multiple dose regimens with SC CNTO 1275 in subjects with moderate to severe psoriasis.	Dose administered as either an initial SC injection or 4 weekly injections.  Group 1: 45 mg SC CNTO 1275 on Day 1; Placebo at Weeks 1, 2, and 3. At Week 16, subjects with PGA $\geq 3$ received 45 mg SC CNTO 1275; Subjects with PGA < 3 received placebo. At Week 20, all subjects received placebo.  Group 2: 90 mg SC CNTO 1275 on Day 1; Placebo at Weeks 1, 2, and 3. At Week 16, subjects with PGA $\geq 3$ received 90 mg SC CNTO 1275; subjects with PGA < 3 received placebo. At Week 20, all subjects received placebo.  Group 3: 45 mg SC CNTO 1275 on Day 1 and at Weeks 1, 2, and 3. At Week 16, subjects with PGA $\geq 3$ received 45 mg SC CNTO 1275; subjects with PGA < 3 received placebo. At Week 20, all subjects received placebo.  Group 4: 90 mg SC CNTO 1275 on Day 1 and at Weeks 1, 2, and 3. At Week 16, subjects with PGA $\geq 3$ received 90 mg SC CNTO 1275; subjects with PGA < 3 received placebo. At Week 20, all subjects received placebo.  Group 5: Placebo on Day 1 and at Weeks 1, 2, and 3. At Week 16, all subjects received placebo. At Week 20, all subjects received 90 mg SC CNTO 1275.	Primary: (1) To evaluate the clinical response to initial single and multiple SC injections of CNTO 1275; (2) To assess the safety of single and multiple SC injections of CNTO 1275 by evaluation of adverse events and laboratory parameters.  Secondary: (1) To evaluate the durability of clinical response; (2) To evaluate the efficacy of retreatment at Week 16 in subgroup of subjects with PGA $\geq 3$ ; (3) To evaluate relationship between PK and PD; (4) To assess PK of single and multiple SC injections of CNTO 1275; (5) To determine immune response to CNTO 1275.	Group 1: 64/55 Group 2: 64/59 Group 3: 64/61 Group 4: 64/58 Group 5: 64/48	Treated through Week 20 with follow-up through Week 52	M: 222 F: 98 45 yrs (18 to 79 yrs)	Plaque psoriasis  Men or women 18 yrs of age or older with plaque psoriasis who were candidates for phototherapy or systemic therapy and had a PASI score $\geq 12$ and at least 10% of total BSA involved.

Best Possible Copy

Appendix A.1 Description of Clinical Efficacy and Safety Studies

Study ID	No. of Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal Study Status	Design & Control Type	Study & Control Drugs Dose, Route, & Regimen(s)	Study Objective(s)	No. of Subjects by Arm Entered/ Completed	Duration of Treatment	Sex Median Age (Range)	Diagnosis Inclusion Criteria
C0743708	48 centers 29 US 16 Canada 3 Belgium	15 Dec 2005 Completed 13 Apr 2007 766 subjects randomized/ 750 planned Study Ongoing (Week 52 Report)	Phase 3, multicenter, randomized, double-blind, placebo-controlled.	<p><b>Group 1:</b> 45 mg SC CNTO 1275 at Week 0, 4, and 16 (q12wks).</p> <p><b>Group 2:</b> 90 mg SC CNTO 1275 at Week 0, 4, and 16 (q12wks).</p> <p><b>Group 3a:</b> Placebo at Weeks 0 and 4; 45 mg SC CNTO 1275 at Weeks 12 and 16 (q12wks).</p> <p><b>Group 3b:</b> Placebo at Weeks 0 and 4; 90 mg SC CNTO 1275 at Weeks 12 and 16 (q12wks).</p> <p><b>Week 28 Dose Interval Adjustment</b> - Week 28 PASI 75 Responders in all groups continued with q12wks dosing.</p> <p>- Week 28 Partial Responders in all groups switched to q8wks dosing.</p> <p>- Week 28 Nonresponders in all groups discontinued dosing.</p> <p><b>Week 40 Randomized Withdrawal</b> Subjects in Groups 1 and 2 responding to their starting regimen at Weeks 28 and 40 (long-term PASI 75 responders) were randomized to:</p> <p>- Maintenance therapy (ie, continued q12wks treatment)</p> <p>- Withdrawal from Therapy (ie, Placebo → Retreatment with original starting regimen) upon loss of 50% of PASI improvement.</p> <p>Subjects in Groups 3a and 3b responding to their starting regimen (PASI 75 responders) received placebo → retreatment with original starting regimen upon loss of 50% of PASI improvement at Week 40.</p>	<p><b>Primary:</b> To evaluate the efficacy and safety of CNTO 1275 in the treatment of subjects with moderate to severe plaque psoriasis.</p> <p><b>Secondary:</b> To evaluate the maintenance of response to CNTO 1275; to evaluate the impact of CNTO 1275 on quality of life.</p>	<p>Subjects through Week 52: 766/666</p> <p>Group 1: 255/215</p> <p>Group 2: 256/224</p> <p>Group 3a: 127/113</p> <p>Group 3b: 128/114</p>	<p>Treated through at least Week 52 with follow-up through the date the last subject completed the Week 52 visit.</p> <p><b>Long Term Extension (Weeks 52 – 264):</b> Subjects will be followed for a total of 5 years from the initial administration of study agent and will continue receiving the same dose and schedule that they were receiving as of the Week 52 database lock. Subjects receiving placebo as of the Week 52 database lock will reinitiate CNTO 1275 upon loss of therapeutic effect at their initial CNTO 1275 treatment regimen followed by maintenance therapy (q12wks treatment).</p>	<p>M: 531 F: 235</p> <p>45.5 yrs (19-76 yrs)</p>	<p>Moderate to severe plaque psoriasis</p> <p>Men or women 18 yrs of age or older who had a PASI ≥ 11, had at least 10% of their total BSA involved, and were considered to be candidates for phototherapy or systemic therapy.</p>

Best Possible Copy

Appendix A.1 Description of Clinical Efficacy and Safety Studies									
Study ID	No. of Study Centers Location(s)	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal Study Status	Design & Control Type	Study & Control Drug: Dose, Route, & Regimen(s)	Study Objective(s)	No. of Subjects by Arm Entered/ Completed	Duration of Treatment	Sex Median Age (Range)	Diagnosis Inclusion Criteria
C0743T09	70 centers 3 Austria 19 Canada 1 France 10 Germany 2 Switzerland 3 UK 32 US	03 Mar 2006 Completed Week 28, 26 Mar 2007 1230 randomized/ 1200 planned Study Ongoing (Week 28 report)	Phase 3, multicenter, randomized, double-blind, placebo- controlled	Group 1: 45 mg SC CNTO 1275 at Weeks 0, 4, and 16 Group 2: 90 mg SC CNTO 1275 at Weeks 0, 4, and 16 Group 3a: Placebo at Weeks 0 and 4; 45 mg SC CNTO 1275 at Weeks 12 and 16 Group 3b: Placebo at Weeks 0 and 4; 90 mg SC CNTO 1275 at Weeks 12 and 16 <u>Week 28 Randomized Dosing Optimization:</u> <u>Week 28 Partial Responders</u> are randomized to: - Continue q12wks dosing, or - Switch to q8wks dosing <u>Week 28 Responders</u> continue with q12wks dosing	Primary: To evaluate the efficacy and safety of CNTO 1275 in the treatment of subjects with moderate to severe plaque psoriasis. Secondary: (1) To evaluate dosing interval adjustment in subjects who inadequately respond to their starting dose regimen and (2) To evaluate the impact of CNTO 1275 on quality of life.	Group 1: 409/591 Group 2: 411/592 Group 3a: 205/190 Group 3b: 205/191	Treated up to Week 16 with follow-up through Week 28.  Long Term Extension (Weeks 52 – 264): Subjects will be followed for a total of 5 years from the initial administration of study agent and will continue receiving the same dose and schedule that they were receiving as of the Week 52 database lock.  After the study is unblinded, dose interval adjustment or dose escalation	M: 240 F: 390  47 yrs (18-86 yrs)	Moderate to severe plaque psoriasis  Men or women 18 yrs of age or older who had PASI $\geq$ 12, have at least 10% total BSA involved, and were considered to be candidates for phototherapy or systemic therapy.

## 5.2 Review Strategy

Best Possible Copy

The applicant is relying on the results from the 2 Phase 3 studies C0743T08 (T08 or PHOENIX 1) and C0743T09 (T09 or PHOENIX 2) to provide the substantial evidence of efficacy to support approval of their product for the proposed indication. The review of efficacy focuses on the primary endpoint: the proportion of subjects who achieved  $\geq 75\%$  improvement in PASI (PASI 75) from baseline at Week 12. Results for the secondary endpoint the Physician's Global Assessment (PGA) will also be discussed. Efficacy outcomes by weight categories will also be discussed as the applicant proposes dosing by weight categories.

*Comment: The Phase 3 trials were underway when the Phase 3 protocols were submitted to the Agency. Elements of the PGA scale (see Appendix 9.6) are of questionable clinical applicability and utility. For example, it is not clear that investigators could determine differences in plaque thickness of 0.25 mm. Additionally, in the reviewer's opinion, a change of 0.25 mm would not be clinically obvious or meaningful.*

The safety review primarily focuses on the integrated safety database wherein the applicant combined the safety data from the Phase 2 study C0379T04 (T04) and the two Phase 3 studies (T08 and T09) for analyses. Data from the Phase 1 studies will be discussed. Additionally, the review will provide discussion of safety data from study of the product in other indications (psoriatic arthritis, Crohn's disease and multiple sclerosis).

### 5.3 Discussion of Individual Studies

The Phase 3 studies were randomized, double-blind, placebo-controlled (through Week 12), and identical in design through Week 28. Enrollment criteria were the same for both studies:

Inclusion Criteria included (see Appendix 9.4 for the complete list):

- 18 years of age or older at time of consent; may be male or female.
- had a diagnosis of plaque-type psoriasis at least 6 months prior to first administration of study agent (subjects with concurrent psoriatic arthritis [PsA] could be enrolled).
- plaque-type psoriasis covering at least 10% of total BSA at screening and at the time of the first administration of study agent.
- PASI score of 12 or greater at screening and at the time of the first administration of study agent.
- candidates for phototherapy or systemic treatment of psoriasis
- agreed not to receive a live virus or live bacterial vaccination during the trial or up to 12 months after the last injection.
- agreed not to receive a BCG vaccination during the trial or up to 12 months after the last injection.
- Be considered eligible according to the following TB screening criteria:
  - a. no history of latent or active TB prior to screening.
  - b. no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
  - c. no recent close contact with a person with active TB or, if there had been such contact, were referred to a physician specializing in TB to undergo additional evaluation and, if warranted, received appropriate treatment for latent TB prior to or simultaneously with the first administration of study agent.
  - d. within 1 month prior to the first administration of study agent, either had a negative tuberculin skin test or had a newly identified positive tuberculin skin test during screening in which active TB had been ruled out and for which appropriate treatment for latent TB had been initiated either prior to or simultaneously with the first administration of study agent.
  - e. had a chest radiograph (both posterior-anterior and lateral views), taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current active TB or old inactive TB.

Exclusion Criteria included (see Appendix 9.4 for the complete list):

- had current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).
- had used any systemic immunosuppressants within 4 weeks of the first administration of study agent
- had received within 3 months prior to the first injection a live virus or bacterial vaccination.
- had a BCG vaccination within 12 months of screening.
- had a history of chronic or recurrent infectious disease,

- had a serious infection or had been hospitalized or received IV antibiotics for an infection during the 2 months prior to screening.
- history of latent or active granulomatous infection, including TB, histoplasmosis, or coccidioidomycosis, prior to screening.
- have had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, *Pneumocystis carinii*, aspergillosis).
- known malignancy or have a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that had been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to the first administration of study agent).

### Study Designs

In both Phase 3 studies subjects were dosed at Weeks 0 and 4 with either placebo, 45 mg of ustekinumab (45 mg) or 90 mg of ustekinumab (90 mg). Primary efficacy was assessed at Week 12 by the proportion of subjects who achieved PASI 75. A major secondary endpoint was the PGA.

At Week 12, subjects initially randomized to placebo treatment were crossed-over to active treatment, receiving either 45 mg or 90 mg of ustekinumab. All subjects received additional doses of ustekinumab at Weeks 16 and 28. Efficacy data were submitted through Week 52 for T08, and the study design from Week 28 is described below. Efficacy data were submitted through Week 28 for T09. Schema for both studies are presented below.

*Comment: For subjects randomized to active treatment at Week 0, the Week 16 dose represented the 1<sup>st</sup> maintenance dose. The Week 12 and 16 doses of ustekinumab received by subjects initially randomized to placebo represented loading doses and corresponded to the Week 0 and 4 doses received by subjects randomized to active treatment at baseline.*

### C0743T08 (T08 or PHOENIX 1)

At Week 28 (“dose optimization”) the following could occur:

- continuation of 45 mg or 90 mg every 12 weeks for subjects with PASI  $\geq 75$  (“responders”)
- escalation of dosing of 45 mg or 90 mg from every 12 weeks to every 8 weeks for PASI 50 to  $< 75$  (“partial responders”)
- discontinuation of dosing if PASI was  $< 50$  (“non-responders”)

At Week 40 (“randomized withdrawal”), the following could occur:

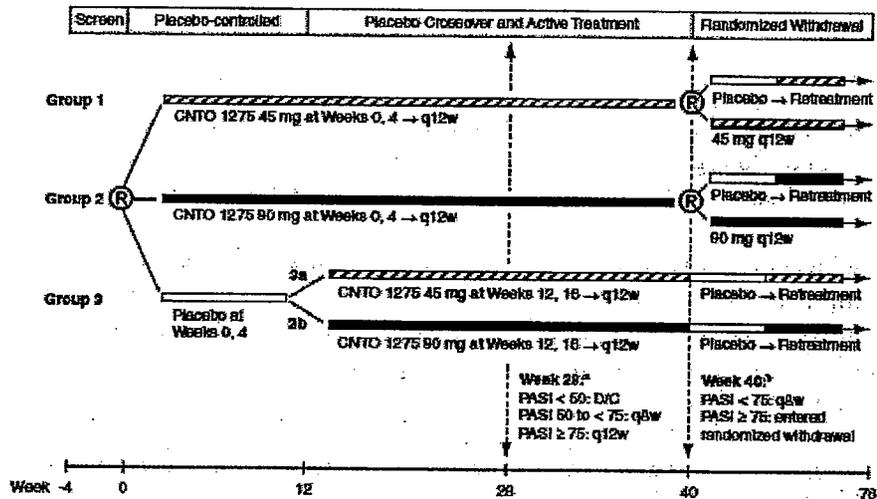
- responders who had been randomized to active treatment at baseline were re-randomized to either
  - continuation of 45 mg or 90 mg dosing every 12 weeks through Week 52 (i.e. one dose) or
  - placebo (with resumption of ustekinumab on loss of PASI 50)
- responders who had been randomized to placebo at baseline were returned to placebo treatment (with resumption of ustekinumab on loss of PASI 50)
- continuation of dosing every 8 weeks for subjects already being dosed at this frequency

- escalation of dosing of 45 mg or 90 mg to every 8 weeks for partial and non-responders

The applicant's intent for the randomized withdrawal of treatment at Week 40 was to allow for the assessment of

- development of tolerance to treatment in subjects who had demonstrated a persistence of PASI 75 through Week 40 (in subjects re-randomized to continue treatment with active at Week 40)
- duration of reponse in subjects who had demonstrated a persistence of PASI 75 through Week 40 (in subjects re-randomized to placebo at Week 40).

Study Design Overview for C0743T08 (T08 or PHOENIX 1)

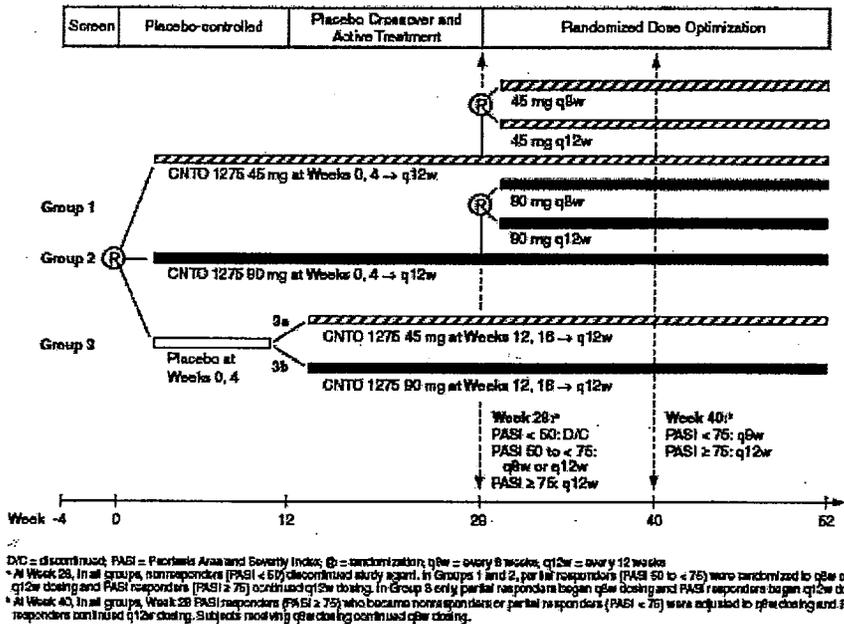


DIC = discontinued, PASI = Psoriasis Area and Severity Index, R = randomized, q8w = every 8 weeks, q12w = every 12 weeks  
 \* At Week 28, in all groups, nonresponders (PASI < 50) discontinued study agent, partial responders (PASI 50 to < 75) began q8w dosing, and PASI responders (PASI ≥ 75) began q12w dosing.  
 † At Week 40, PASI responders to q12w dosing in Groups 1 and 2 were randomized to either placebo or continued q12w CANTO 1275 (at their original dose), while those in Group 3 received placebo. At time 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 q8w dosing. Subjects receiving q8w dosing continued q8w dosing.

Best Possible Copy

C0743T09 (T09 or PHOENIX 2)

Study Design Overview for C0743T09 (T09 or PHOENIX 2)

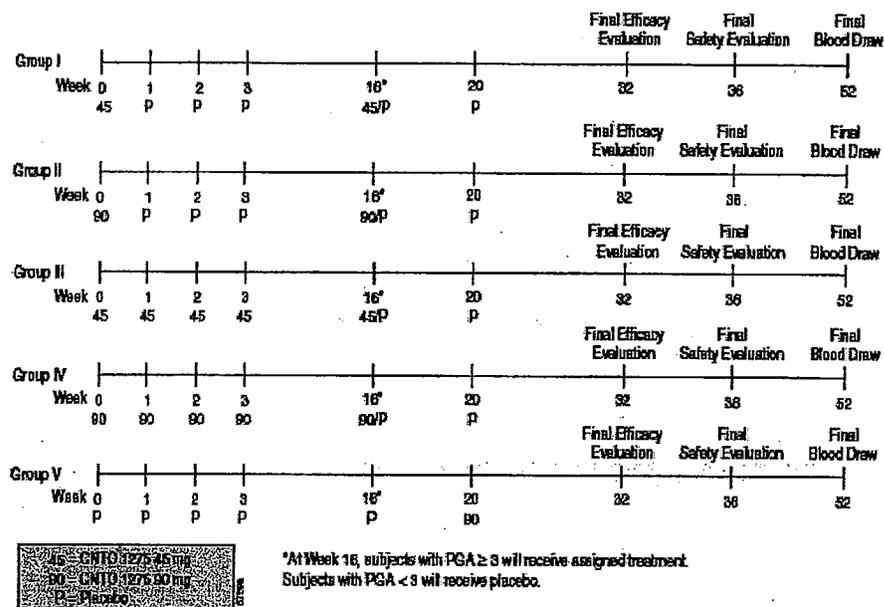


Best Possible Copy

C0379T04 (T04)

Data from study T04 were combined with data from the Phase 3 studies in the integrated safety database and were not relied on to support efficacy. This was a Phase 2 study, and 45 mg and 90 mg dosing were evaluated. However, the dosing regimens differed from those evaluated in the Phase 3 studies and proposed in labeling.

**Study Design Overview for C0379T04**



**6 Review of Efficacy**

**Efficacy Summary**

**6.1 Indication**

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

**6.1.1 Methods**

The efficacy review will discuss outcomes from the Phase 3 studies T08 and T09 as these are the studies on which the applicant is relying to provide the substantial evidence of efficacy to support approval.

**6.1.2 Demographics**

Baseline characteristics of the study population are presented in the following tables from the Integrated Summary of Efficacy (ISE):

**Summary of demographics at baseline; subjects randomized at Week 0 in psoriasis Phase 3**  
**Source: Appendix B.3 of ISE**

	T08	T09
Subjects randomized at Week 0	n= 766	n=1230
Sex		
n	766	1230
Male	531 (69.3%)	840 (68.3%)
Female	235 (30.7%)	390 (31.7%)
n	766	1230
Caucasian	717 (93.6%)	1128 (91.7%)
Black	14 (1.8%)	27 (2.2%)
Asian	20 (2.6%)	50 (4.1%)
Other	15 (2.0%)	25 (2.0%)
Age (yrs)		
n	766	1230
Mean ± SD	45.3± 11.71	46.2 ± 12.24
Median	45.5	47.0
IQ range	(37.0, 53.0)	(38.0, 55.0)
Range	(19, 76)	(18, 86)
Weight (kg)		
n	766	1229
Mean ± SD	93.88 ± 23.685	90.99 ± 21.278
Median	91.60	88.60
IQ range	(76.80, 107.50)	(76.00, 103.80)
Range	(46.9, 183.2)	(138, 201)
Height (cm)		
n	766	1230
Mean ± SD	172.0 ± 10.05	172.2 ± 9.61
Median	173.0	173.0
IQ range	(165.0, 179.0)	(165.0, 179.0)
Range	(132, 201)	(138, 201)
BMI		
n	766	1229
Normal (< 25)	118 (15.4%)	245 (19.9%)
Overweight (25 to < 30)	262 (34.2%)	390 (31.7%)
Obese (≥30)	386 (50.4%)	594 (48.3%)
Geographic region		
n	766	1230
Europe	13 (1.7%)	215 (17.5%)
Canada	371 (48.4%)	599 (48.7%)
US	382 (49.9%)	416 (33.8%)

*Comment: Overall, baseline demographics were similar in the 2 studies. Most subjects were male, Caucasian, of approximately 45 years of age and overweight to obese. These demographic characteristics are consistent with what is known about the psoriasis population.*

**Baseline Disease Characteristics Source Appendix B.4 f ISE**

	PHOENIX 1	PHOENIX 2
Subjects randomized at Week 0	766	1230
Psoriasis disease duration (yrs)		
n	766	1230
Mean ± SD	19.92 ± 11.460	20.1 ± 12.07
Median	18.33	18.5
IQ range	(11.16, 28.16)	(10.4, 27.6)
Range	(0.6, 58.1)	(0, 64)
Age at diagnosis (yrs)		
n	766	1230
Mean ± SD	25.4 ± 13.15	26.2 ± 13.64
Median	23.0	24.0
IQ range	(16.0, 34.0)	(16.0, 35.0)
Range	(0, 74)	(0, 85)
BSA (%)		
n	766	1230
Mean ± SD	26.7 ± 16.70	26.4 ± 16.81
Median	21.0	20.0
IQ range	(15.0, 33.0)	(14.0, 32.0)
Range	(10, 96)	(10, 98)
BSA		
n	766	1230
≥ 20%	421 (55.0%)	662 (53.8%)
< 20%	345 (45.0%)	568 (46.2%)
PASI score (0-72)		
n	766	1230
Mean ± SD	20.22 ± 8.287	19.61 ± 7.265
Median	17.60	17.50
IQ range	(14.50, 32.60)	(14.40, 22.50)
Range	(12.0, 62.0)	(12.0, 60.0)
PASI score		
n	766	1230
≥ 20	260 (33.9%)	433 (35.2%)
< 20	506 (66.1%)	797 (64.8%)
PGA score		
n	765	1230
Cleared (0)	0 (0.0%)	0 (0.0%)
Minimal (1)	0 (0.0%)	0 (0.0%)
Mild (2)	42 (5.5%)	96 (7.8%)
Moderate (3)	388 (50.7%)	646 (52.5%)
Marked (4)	298 (39.0%)	424 (34.5%)
Severe (5)	37 (4.8%)	64 (5.2%)
PGA score		
n	765	1230
Marked or severe (≥ 4)	335 (43.8%)	488 (39.7%)

Psoriatic arthritis

History of PsA

258 (33.7%)

305 (24.8%)

**Comment:** Overall, baseline disease characteristics were comparable between studies. Most subjects had disease severity well beyond the minimum 10% BSA involvement required by the Inclusion Criteria, and the mean PASI was higher than the 12 required for study eligibility.

### 6.1.3 Patient Disposition

A total of 984 subjects were screened, and 766 subjects were randomized to treatment in study T08. One subject in study T08 was randomized in error and received no study treatment (was randomized to the 90 mg group). A total of 1567 subjects were screened, and 1230 subjects were randomized to treatment in study T09. All randomized subjects received treatment in study T09. Subject randomization to treatment groups is presented in the following Table.

**Patient Disposition (Sources: Figure 2 of study reports for T08 and T09)**

Number randomized	Placebo	45 mg	90 mg
T08 (n=766)	255	255	256
T09 (n=1230)	410	409	411

### 6.1.4 Analysis of Primary Endpoint(s)

As stated, the primary endpoint was the proportion of subjects who achieved  $\geq 75\%$  improvement from baseline in PASI at Week 12 (PASI 75). The following table presents the results of the applicant's analyses of the primary endpoint:

**PASI 75 responders at Week 12 (ITT)**

**(Sources Table 9 of the study report for T08 and Table 8 of the study report for T09)**

	Placebo	45 mg	90 mg
<b>T08</b>	n=255	n=255	n=256
	8 (3.1%)	171 (67.1%)	170 (66.4%)
p-value		< 0.001	< 0.001
<b>T09</b>	n=410	n=409	n=411
	15 (3.7%)	273 (66.7%)	311 (75.7%)
p-value		< 0.001	< 0.001

Dr. Fritsch's analyses for the primary endpoint yielded results that were in agreement with the applicant's. From the statistical review:

**Table 1 – Week 12 Efficacy Results (Study 08)**

	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
<b>ITT</b>	N=255	N=256	N=255
PASI 75 Response	171 (67%) p<0.001	170 (66%) p<0.001	8 (3%)
PGA Cleared or Minimal	154 (60%) p<0.001	158 (62%) p<0.001	10 (4%)
<b>Per Protocol</b>	N=255	N=251	N=250
PASI 75 Response	171 (67%) p<0.001	170 (68%) p<0.001	8 (3%)
PGA Cleared or Minimal	154 (60%) p<0.001	158 (63%) p<0.001	10 (4%)

**Table 2 – Week 12 Efficacy Results (Study 09)**

	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
<b>ITT</b>	N=409	N=411	N=410
PASI 75 Response	273 (67%) p<0.001	311 (76%) p<0.001	15 (4%)
PGA Cleared or Minimal	278 (68%) p<0.001	302 (73%) p<0.001	20 (5%)
<b>Per Protocol</b>	N=405	N=406	N=399
PASI 75 Response	272 (67%) p<0.001	311 (76%) p<0.001	15 (4%)
PGA Cleared or Minimal	277 (68%) p<0.001	302 (74%) p<0.001	20 (5%)

**Comment:** Primary efficacy has been demonstrated for both doses in both studies. Results for ustekinumab-treated subjects were similar between dosing groups and across studies, with the exception of the 90 mg group in study T09 in which a higher proportion of subjects achieved success as compared to the 45 mg group and both active groups in study T08. The Advisory Committee voted unanimously that the applicant provided sufficient information to demonstrate efficacy of ustekinumab in the treatment of plaque psoriasis..

#### 6.1.5 Analysis of Secondary Endpoints(s)

The proportion of subjects with a PGA score of cleared (0) or minimal (1) at Week 12 was a major secondary endpoint:

PGA score of cleared (0) or minimal (1) at Week 12

Inclusion criteria did not specify a level of disease severity by the PGA scale, although this assessment was done at baseline. The following table presents the results of the applicant's analyses of the major secondary endpoint:

**Applicant's Results for PGA**

(Sources: Table 10 of study report for T08 & Table 9 of study report for T09)

	Placebo	45 mg	90 mg
<b>T08</b>	n=255	n=255	n=256
PGA of clear (0) or minimal(1)			
p-value	10 (3.9%)	154 (60.4%) < 0.001	158 (61.7%) < 0.001
<b>T09</b>	n=410	n=409	n=411
PGA of clear (0) or minimal(1)	20 (4.9%)	278 (68.0%) < 0.001	302 (73.5%) < 0.001
p-value			

*Comment: Efficacy has been demonstrated for both doses in both studies as assessed by the major secondary endpoint, the PGA. Results were similar between dosing groups (for ustekinumab-treated subjects) in study T08. In study T09, the results were higher in both active groups compared to outcomes in study T08. Again, the highest proportion of subjects achieved success was in the 90 mg group in study T09. Dr. Fritsch's analyses of the PGA are presented above in Section 6.1.4 and are in general agreement with the applicant's (see the results of her analyses for this endpoint in the table in the discussion of primary efficacy).*

The change in DLQI from baseline at Week 12 was also a pre-specified major secondary endpoint; however, these outcomes will not be presented,

\_\_\_\_\_

\_\_\_\_\_

b(4)

6.1.6 Other Endpoints

The applicant evaluated the following endpoints (among numerous others) in study T08:

- Nail Psoriasis Severity Index,
- a Nail PGA and
- # of nails involved.

- change from baseline in the itch Visual Analog Scale (VAS)

The Nail Psoriasis Severity Index (NAPSI) measures the severity of nail involvement, and the

b(4)

### 6.1.7 Subpopulations

The proportion of PASI 75 responders at Week 12 was calculated for the following subgroups: Gender, Race, Age at screening (< 45 years old, ≥45 to 65 years old, ≥65 years old), body mass index [BMI; normal (< 25 BMI), overweight (≥25 and < 30 BMI), obese (≥30 BMI)], and Geographic region.

**Proportion of Subjects Achieving a PASI 75 Response at Week 12 by Subgroups Study T08 (Source: Figure 19 of study report for T08)**

	Placebo (%)	Ustekinumab (%)
All subjects	255 (3.1)	511 (66.7)
Gender		
Male	183 (1.1)	348 (62.9)
Female	72 (8.3)	163 (74.8)
Race		
Caucasian	235 (2.6)	482 (66.4)
Black	4 (50.0)	10 (80.0)
Asian	12 (0.0)	8 (50.0)
Other	4 (0.0)	11 (81.8)
Age		
< 45	126 (4.0)	234 (70.1)
≥45 to < 65	119 (2.5)	253 (64.0)
≥65	10 (0.0)	24 (62.5)
BMI		
Normal (< 25)	39 (10.3)	79 (73.4)
Overweight (≥25 to < 30)	98 (3.1)	164 (68.3)
Obese (≥30)	118 (0.8)	268 (63.8)
Geographic region		
Europe	3 (0.0)	10 (60.0)
Canada	122 (3.3)	249 (65.9)
United States	130 (3.1)	252 (67.9)

**Proportion of Subjects Achieving a PASI 75 Response at Week 12 by Subgroups Study T09**  
 (Source: Figure 14 of study report for T09)

	Placebo (%)	Ustekinumab (%)
All subjects	410 (3.7)	820 (71.2)
Gender		
Male	283 (2.1)	557 (67.9)
Female	127 (7.1)	263 (78.3)
Race		
Caucasian	381 (3.9)	747 (70.5)
Black	9 (0.0)	18 (72.2)
Asian	12 (0.0)	35 (74.3)
Other	5 (0.0)	20 (90.0)
Age		
< 45	179 (5.0)	365 (73.2)
≥45 to < 65	197 (2.0)	413 (71.4)
≥65	34 (5.9)	42 (52.4)
BMI		
Normal (< 25)	80 (5.0)	165 (79.4)
Overweight (≥25 to < 30)	135 (2.2)	255 (74.9)
Obese (≥30)	195 (4.1)	399 (65.7)
Geographic region		
Europe	73 (1.4)	142 (69.0)
Canada	196 (3.6)	403 (77.9)
United States	141 (5.0)	275 (62.5)

*Comment: For both Phase 3 studies, results for PASI 75 outcomes for each of the presented subgroups were generally consistent with the overall results from the Phase 3 studies.*

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant proposes fixed weight-based dosing by two weight categories:

- for patients weighing ≤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.

The applicant did not conduct dose-ranging studies. In the Summary of Clinical Efficacy (Section 4), the applicant states that these regimens were selected “because the Phase 2 results predicted that they would provide exposures necessary to achieve efficacy levels in the middle range of the dose-response curve of efficacy.”

The Pharmacometrics reviewer, Pravin Jadhav, Ph.D., performed exposure-response analyses (ustekinumab-AUC-PASI 75) to evaluate the applicant’s proposed weight-based dosing regimens, and he reported the key findings as being:

1. “Psoriasis improvement is dependent on serum ustekinumab concentration or AUC.
2. “At a given dose, serum concentrations (and AUCs) in heavier (median body weight 117 kg) subjects are 50% compared to those in lighter subjects (median body weight 68 kg).
3. “Due to PK differences, the (PASI 75) response rate in heavier subject is lower than response rate in lighter subjects.”

The relationship between weight, dose and outcomes was borne out in the Phase 3 studies as seen by the efficacy outcomes when presented by weight quartiles and 10 kg increments and dosing groups:

**PASI 75 responders by body weight (Source: Appendix B.8 of ISE)**

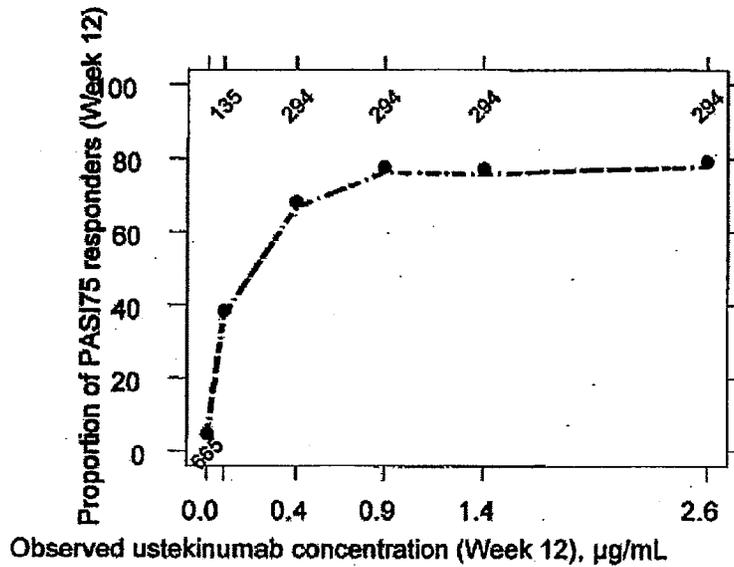
**Appendix B.8** Number of PASI 75 responders at Week 12 by body weight (kg) categories; subjects randomized at Week 0 in psoriasis Phase 3

	Placebo	CNTO 1275	
		45 mg	90 mg
Subjects randomized at Week 0	665	664	667
PASI 75 responders at Week 12	23 (3.5%)	444 (66.9%)	481 (72.1%)
<b>Body weight (kg) by quartiles</b>			
≤ 75	5.8% (9/155)	78.1% (125/160)	80.9% (114/141)
> 75 to ≤ 90	3.3% (6/181)	71.0% (130/183)	70.4% (140/199)
> 90 to ≤ 105	2.4% (4/168)	68.8% (110/160)	69.2% (110/159)
> 105	2.5% (4/161)	49.1% (79/161)	70.1% (117/167)
<b>Body weight (kg) by fixed intervals</b>			
≤ 50	16.7% (1/6)	87.5% (7/8)	100.0% (6/6)
> 50 to ≤ 60	12.9% (4/31)	92.9% (26/28)	82.8% (24/29)
> 60 to ≤ 70	4.3% (3/70)	71.2% (47/66)	82.8% (48/58)
> 70 to ≤ 80	2.2% (2/89)	75.0% (93/124)	75.0% (81/108)
> 80 to ≤ 90	3.6% (5/140)	70.1% (82/117)	68.3% (95/139)
> 90 to ≤ 100	2.5% (3/120)	71.3% (87/122)	69.0% (78/113)
> 100 to ≤ 110	2.5% (2/80)	55.8% (43/77)	73.3% (63/86)
> 110 to ≤ 120	1.7% (1/59)	42.0% (21/50)	66.2% (43/65)
> 120 to ≤ 130	4.0% (1/25)	67.7% (21/31)	84.2% (16/19)
> 130	2.2% (1/45)	41.5% (17/41)	62.8% (27/43)

**Comment:** 1) Outcomes in weight quartiles between treatment groups were similar in ustekinumab-treated subjects until the heaviest category, where there is clear separation of efficacy outcomes for subjects > 105 kg dosed with 45 mg compared to those dosed with 90 mg. Also, efficacy outcomes progressively decreased as weight increased in the 45 mg group. A similar pattern is evidenced when results are broken out by 10 kg increments: again, there is clear separation at the >100 kg to ≤100 kg category when 45 mg group is compared to the 90 mg group. 2) The outcomes in lower weight subjects (e.g. ≤60 kg) treated with ustekinumab suggest that efficacy could be seen in some of these subjects with doses less than 45 mg. The applicant did not explore this. However, efficacy outcomes for placebo-treated subjects were also noticeably higher in subjects ≤60 kg relative to outcomes for placebo-treated subjects in heavier weight categories.

The proportion of PASI responders correlated with serum concentrations of ustekinumab. This relationship is demonstrated in Figure 4 from Dr. Jadhav's review:

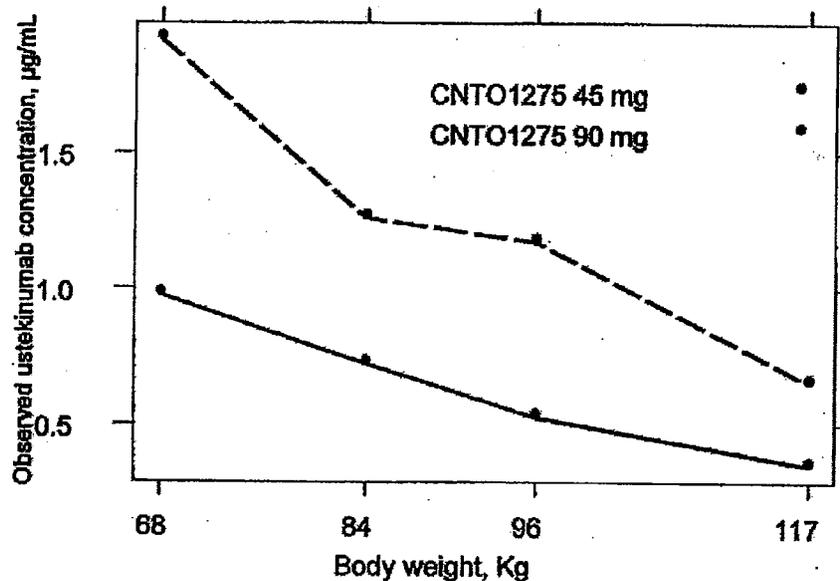
**Figure 4: Relationship between serum ustekinumab concentration and proportion of PASI75 responders at week 12 (upper panel) and PGA responders at week 12 (lower panel). Placebo treated subjects and subjects with undetectable ustekinumab concentrations were plotted at ~0.1 µg/mL (0.085 µg/mL; 50% of lower limit of quantification), 0 µg/mL, respectively. Subjects with missing pharmacokinetic data at a given visit were ignored. The numbers corresponding to each quantile represent # of subjects. The numbers represent # of subjects in each quantile.**



The remainder of this page is left intentionally blank.

A relationship was also seen between serum concentration and weight. At a given dose, lower weight subjects had higher serum concentrations of ustekinumab than did higher weight subjects (twice as high). The relationship between serum concentration and weight is demonstrated in Figure 11 from Dr. Jadhav's review (45 mg is represented by the solid line and 90 mg the dotted line):

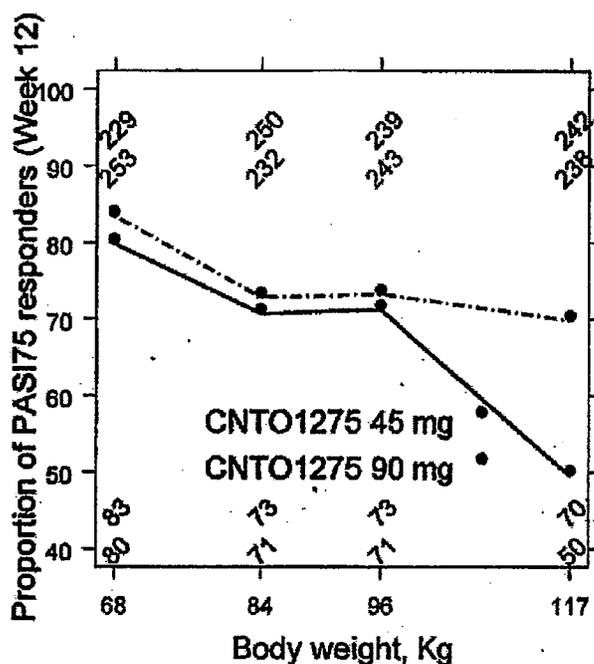
**Figure 11: Observed ustekinumab concentration at Week 12 by body weight quantiles in subjects randomized at Week 0.**



The remainder of this page is left intentionally blank.

Dr. Jadhav demonstrates the relationship between weight, dose and outcomes in Figure 10 from his review, as was also revealed in the applicant's analyses (45 mg is represented by the solid line and 90 mg the dotted line):

**Figure 10: Proportion of PASI75 responders at Week 12 by body weight quantiles from combined week 12 and 24 data in subjects randomized at Week 0 and placebo crossover. The numbers represent response rate (bottom) and # of subjects (top) at each quantile.**



*Comment: Dr. Jadhav's analyses support that some weight-based approach to dosing of ustekinumab is both reasonable and appropriate (for maximizing efficacy outcomes). However, the applicant did not evaluate other weight-based dosing regimens. It is possible that the interrelations between pharmacokinetics, PASI 75 outcomes and weight could be more completely addressed by dosing regimens alternative to the applicant's proposed dosing by weight categories of  $\leq 100$  kg and  $> 100$  kg.*

Dr. Jadhav employed the applicant's population pharmacokinetic model to derive AUCs in individual subjects then used these data to develop a model to evaluate other dosing regimens. The objective of these analyses was "to derive a regimen that might yield optimal PASI75 response rate for entire population." Based on his analyses, Dr. Jadhav recommended a three-step dosing regimen which is discussed below.

*Comment: This review will discuss only the dosing regimen recommended by Dr. Jadhav and how it compares to the applicant's proposed dosing recommendations. The reader is referred to*

*Dr. Jadhav's review for discussion of other dosing regimens that were explored under these analyses.*

**Predicted response rates under different dosing regimens based on the AUC-proportion of PASI75 responders model (Source: Table 5 of Dr. Jadhav's review)**

Dosing strategy	Dose	Weight-Based Dosing Adjustments			
		Predicted proportion (%) (Overall and by weight cut-offs)			
		Overall	70 kg	≥70-<100 kg	≥100 kg
Applicant's Two-Step	<100kg: 45 mg ≥100kg: 90mg	70	80	68	70
Alternative Three-step	<70kg: 45mg ≥70-<100kg: (0.75mL) 67.5mg ≥100kg: 90mg	73	80	74	70

*Comment: Subjects who would potentially benefit from the three-step weight-based dosing approach would be "mid-weight" subjects ≤70 kg and <100 kg (outcomes highlighted in above table). While a compelling case for the three-step dosing regimen can be made (as has been done by Dr. Jadhav), the reviewer recommends the two-step approach proposed by the applicant. Dr. Jadhav's analyses have convincingly demonstrated that the two-step regimen may not represent the optimal regimen for maximizing efficacy. However, in the reviewer's opinion, the projected outcomes for "mid-weight" patients administered 67.5 mg are not sufficiently higher than those demonstrated with dosing of 45 mg to recommend the increased exposure to ustekinumab to all subjects in this mid-weight category, when most are likely to achieve satisfactory outcomes with less exposure to ustekinumab. The reviewer acknowledges that in the development program, some subjects < 100 were exposed to 90 mg, i.e. a higher dose than proposed under the alternative three-step regimen, and no safety signals emerged with the higher exposures. Additionally, the reviewer suspects that in clinical practice, there will be patients who get results under the two-step regimen with which they are completely satisfied, but that might fall short of PASI 75, the benchmark commonly employed in clinical studies. PASI 50, for example, has been reported by some to be a clinically meaningful outcome.<sup>10</sup>*

*The Advisory Committee voted 7 to 3 in favor of the two-step regimen proposed by the applicant.*

Self Administration

After Week 12 and at the discretion of the investigator and subject, the protocols for the Phase 3 studies allowed for self-administration at the investigative site "under the supervision of an appropriately licensed and authorized health professional." Thus, the only data provided in support of self-administration reflect such being done under medical supervision.

b(4)

**Comment:** *As subjects self-injected under medically-supervised conditions, the applicant has no data from real-world use conditions, i.e. self-administration without benefit of supervision of by a health-care professional. Therefore, the applicant lacks adequate data to support self-administration.*

*The reviewer acknowledges that the technical complexities of subcutaneous injections are few. Self injections are done daily by many patients who suffer from chronic diseases. Unlike insulin-dependent diabetics, for example, who would have daily experience with self-administration of subcutaneous injections, the applicant's product is proposed for maintenance dosing every 12 weeks (i.e. every 3 months or 4 times per year). With such infrequency, it is unclear to what extent patient's might develop adequate experience with injection-associated procedures, and poor technique could have implications for both safety and efficacy outcomes. Additionally, this is a first-in-class product about which we are all very much still learning. In the reviewer's opinion, it is premature even inappropriate to introduce it into the marketplace with self-administration as an option at launch. The reviewer considers it reasonable to reconsider self administration once more safety data are available and if the applicant were to provide adequate use data to support the option of self-administration (e.g. real-world use).*

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The development program provided limited information regarding persistence of efficacy and/or tolerance effects. These effects were evaluated in the randomized withdrawal segment of study T08.

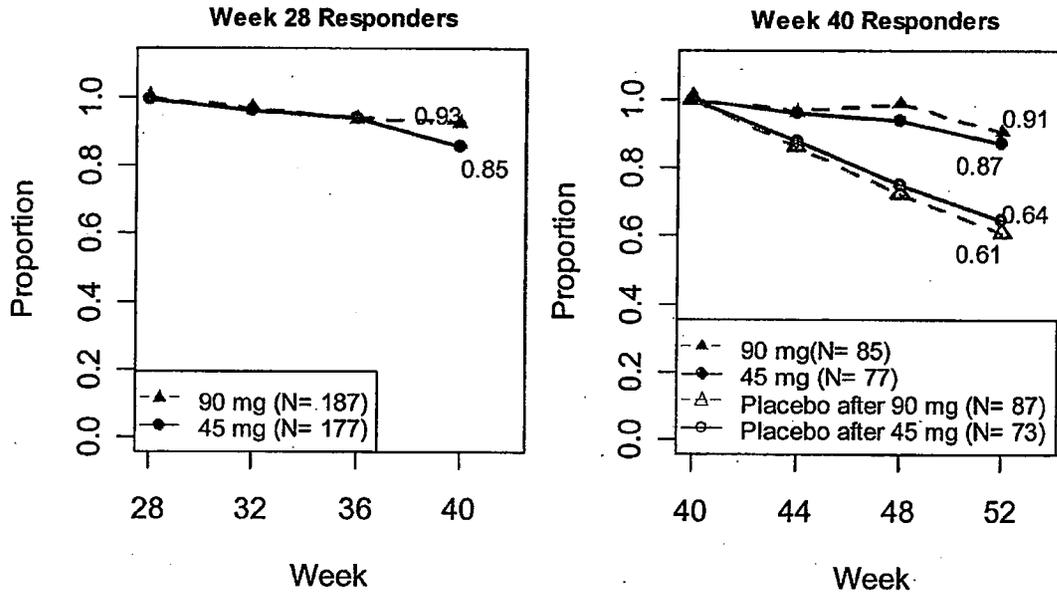
Tolerance was assessed in subjects randomized to ustekinumab at Week 0 and re-randomized at Week 40 to continue ustekinumab (every 12 weeks). The application included data through Week 52 for evaluation of tolerance for only 77 of 255 (30%) of subjects in the 45 mg group and 85 of 256 (33%) in the 90 mg group. From Dr. Fritsch's statistical review:

**Table 3 – Week 40 Dosing Status for Subjects Originally Randomized to Ustekinumab (Study 08)**

Regimen	45 mg N=255	90 mg N=256
Always every 12 weeks (Responder at Weeks 28 and 40)	77 (30%)	85 (33%)
Every 12 weeks/Withdrawal at Week 40 (Responder at Weeks 28 and 40)	73 (29%)	87 (34%)
Accelerated to every 8 weeks (Partial Responder at Week 28 or 40)	72 (28%)	56 (22%)
Terminated (Non-Responder at Week 28)	17 (7%)	5 (2%)
Dropouts	16 (6%)	23 (9%)

The following table presents outcomes for long-term PASI 75 subjects randomized at Week 40 to either continue active treatment every 12 weeks or switch to placebo.

Figure 1 from the statistical review– Maintenance of PASI 75 Response among Subjects Responding at Weeks 28 and 40 (Study 08)



Source: Attachment 3.7 from study report for T08

Attachment 3.7 Summary of maintenance of PASI 75 response; subjects randomized at Week 40

	CNTO 1275					
	45 mg		90 mg		Combined	
	Placebo	q12 wks	Placebo	q12 wks	Placebo	q12 wks
Subjects randomized at Week 40	73	77	87	85	160	162
Maintenance response rate, % (95% CI) <sup>a</sup>						
Through Week 44	87.7 (80.1, 95.2)	96.1 (91.8, 100.0)	86.2 (79.0, 93.5)	96.5 (92.5, 100.0)	86.9 (81.6, 92.1)	96.3 (93.4, 99.2)
Through Week 48	74.0 (63.9, 84.0)	93.5 (88.0, 99.0)	73.5 (64.2, 82.8)	95.3 (90.8, 99.8)	73.7 (66.9, 80.5)	94.4 (90.9, 98.0)
Through Week 52	64.4 (53.4, 75.4)	87.0 (79.5, 94.5)	59.5 (49.1, 69.8)	87.1 (79.9, 94.2)	61.7 (54.2, 69.3)	87.0 (81.9, 92.2)
Through Week 56	55.1 (43.4, 66.7)	83.8 (75.4, 92.3)	49.2 (38.2, 60.2)	87.1 (79.9, 94.2)	51.9 (43.9, 60.0)	85.5 (80.1, 91.0)
p-value		< 0.001		< 0.001		< 0.001

<sup>a</sup> Based on Life-table estimates using all data collected through the date the last subject completed Week 52.

**Comment:** In the reviewer's opinion, the data do not adequately address the question of tolerance as the randomized withdrawal period only evaluated subjects through one maintenance dose (from Week 40 to Week 52), and tolerance could develop beyond this time point.

From Dr. Fritsch's Figure 9 and the applicant's Attachment 3.7, approximately, 60% of subjects in the placebo group had PASI 75 at Week 52. A PASI 75 at this time point means that most placebo-treated subjects had maintained a PASI 75 response from Week 28, the time of their last dose of ustekinumab. From Attachment 3.7, it is noted too that approximately 52% of subjects in the placebo groups had a PASI 75, at Week 56 (i.e. 28 weeks after their last dose of

*ustekinumab). This suggests that approximately 50% of responders may maintain PASI 75 response well beyond the 12-week time point (i.e. the maintenance dosing schedule) that maintenance dosing at longer intervals could be appropriate for at least some (and perhaps most) patients. Additionally, even for subjects who lose a PASI 75 response, the extent of disease recurrence may not be sufficiently extensive to necessitate re-treatment with a systemic agent (e.g. ustekinumab) and may be of sufficiently limited extent that it could be managed with alternative, more conservative treatment (e.g. topicals). A loss of PASI 75 represents a loss of efficacy by the definition in these clinical studies, but may not necessarily translate to a degree of loss of effect that may require only limited intervention. It is possible too that treatment effect could be recaptured or maintained with a lower dose than required to bring the disease under initial control. Therefore, maintenance treatment has not been adequately evaluated.*

#### 6.1.10 Additional Efficacy Issues/Analyses

In study T08, 39 subjects who lost  $\geq 50\%$  of their Week 40 PASI after having treatment withdrawn had ustekinumab treatment reinitiated (restarted at original dose) and were followed for at least 4 weeks. Per Attachment 3.38 of the study report for T08, 4 weeks following re-initiation of therapy, 17 of 39 subjects (43.6%) achieved a PASI 75 response, 8 weeks after re-initiation of therapy, 16 of 21 (76.2%) of subjects achieved a PASI 75 response and at 12 weeks after re-initiation of therapy 6 of 7 subjects had achieved PASI 75.

*Comment: The numbers of subjects are too few to adequately speak to the response to re-initiation of treatment following loss of response.*

## 7 Review of Safety

### Safety Summary

#### 7.1 Methods

The applicant conducted five studies in subjects with psoriasis, and this constitutes the clinical development program for this indication. For the Integrated Summary of Safety (ISS), the applicant combined the data from three studies (see Section 7.1.1 below). Additionally, the applicant included safety data from study of their product for Crohn's disease, psoriatic arthritis and multiple sclerosis.

For the ISS, the applicant generally analyzed and presented the safety data by 2 study periods: 1) through Week 12 (reflecting placebo-controlled portions of the 3 studies) and 2) through the end of the reporting period. The duration of follow-up differed for all 3 studies; therefore, "through the end of the reporting period" represents:

- through Week 36 for study T04.
- through Week 52 for study T08.
- through Week 28 for study T09.

*Comment: For "through the end of the reporting period", data for the placebo group reflect shorter durations of follow-up compared to durations of follow-up for subjects in ustekinumab groups. This is because the placebo-controlled period was through Week 20 for the Phase 2*

*study and through Week 12 for the Phase 3 studies. For example, for subjects randomized to placebo at Week 0 in study T08, the duration of follow-up reflects through Week 12; for subjects randomized to ustekinumab at Week 0 in T08, the duration of follow-up reflects through Week 52. To account for the different durations of follow-up, the applicant adjusted some analyses of adverse events per hundred subject-years.*

Data through the end of the reporting period were presented by the following categories:

- Placebo: reflecting Weeks 0 to 20 in the Phase 2 study, and Weeks 0 to 12 in the Phase 3 studies.
- Placebo → 45 mg: for subjects who crossovered from placebo to 45 mg.
- Placebo → 90 mg: for subjects who crossovered from placebo to 90 mg.
- 45 mg: subjects who received ustekinumab 45 mg from Week 0.
- 90 mg: subjects who received ustekinumab 90 mg from Week 0.
- Combined: all subjects who received ustekinumab

### 7.1.1 Clinical Studies Used to Evaluate Safety

The safety database in the ISS primarily consists of three studies: one Phase 2 study, C0379T04 (T04) and two Phase 3 studies C0473T08 (T08 or Phoenix 1) and C0473T09 (T09 or Phoenix 2). The following table presents the number of subjects evaluated in each study:

Studies in the Integrated Summary of Safety		Source: Table 1 of ISS
Study	Dosing Regimen (#Subjects treated)	
C0379T04 52 weeks (20-week placebo period)	Fixed doses: - Placebo (n = 64) - Placebo → 90 mg single dose (n = 49) - 45 mg single SC dose (n = 63) - 90 mg single SC dose (n = 64) - 45 mg weekly x 4 SC doses (n = 63) - 90 mg weekly x 4 SC doses (n = 62)	
C0743T08 ≥52 weeks (12-week placebo period)	Fixed doses: - Placebo (n = 255) - Placebo → 45 mg (n = 123) - Placebo → 90 mg (n = 120) - 45 mg SC Weeks 0, 4 then q12w (n = 255) - 90 mg SC Weeks 0, 4 then q12w (n = 255)	
C0743T09 28 weeks (12-week placebo period)	Fixed doses: - Placebo (n = 410) - Placebo → 45 mg (n = 197) - Placebo → 90 mg (n = 195) - 45 mg SC Weeks 0, 4 then q12w (n = 409) - 90 mg SC Weeks 0, 4 then q12w (n = 411)	

### 7.1.2 Adequacy of Data

An adequate number of subjects were exposed to the new product under the proposed dosing regimen to reasonably characterize the short-term safety of the product under conditions of

intended use. In the reviewer's opinion, all clinical evaluations that were reasonably applicable were conducted to assess the safety of the product in the proposed target population.

The numbers of subjects exposed to the product at dosage levels intended for clinical use for the periods of six months and one year exceeded those recommended in the ICH E1A guideline to characterize the long-term safety of a product intended for treatment of a non-life-threatening condition. (Those numbers are 300 to 600 subjects for six months and 100 subjects for one year.) However, ICH E1A also states that larger safety databases may be needed to make risk/benefit decisions in certain situations. Given the theoretical risk of malignancy and the long latency period for and presumed low frequency of development, it is unclear what numbers of subjects followed for what duration would be sufficient to characterize this risk. Additionally, the numbers of subjects in the safety database and their duration of follow-up may not be sufficient to characterize the risk of particular infectious events.

### 7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Although different dosing regimens were evaluated in the Phase 2 study than were evaluated in the Phase 3 studies (in which the dosing regimens proposed for the marketplace were evaluated), all 3 studies evaluated 45 mg and 90 mg in subjects with moderate to severe psoriasis defined as PASI  $\geq 12$  and at least BSA  $\geq 10\%$  involvement. (The reader is also referred to Section 7.1.1.)

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 2,266 subjects received ustekinumab in the 3 studies pooled for the ISS:

- 1,110 subjects received 45 mg (320 of whom received placebo for the first 12 weeks);
- 1,156 subjects received 90 mg (364 of whom received placebo for the first 12 weeks).

Subjects were considered to have had at least 6 months of exposure if the interval between the first and last doses of ustekinumab was at least 14 weeks and at least a year of exposure if the interval between the first and last doses of ustekinumab was at least 38 weeks. The numbers of subjects exposed and the durations of exposures are presented in the following table:

**Numbers of subjects exposed and durations of exposure through the end of the reporting period**

	45 mg N= 1110	90 mg n= 1156
Duration of ustekinumab exposure		
At least 6 months	812 (73.2%)	790 (68.3%)
At least 1 year	191 (17.2%)	171 (14.8%)
Avg number of injections administrations	3.4	3.2
Mean dose $\pm$ SD	153.0 $\pm$ 64.7	288.7 $\pm$ 129.3
Range	(45, 360)	(45, 720)

Source: Table 3 from the ISS

Clinical Review  
Brenda Carr, M.D.  
BLA 125261  
Ustekinumab

---

*Comment: The definitions of exposure reflected the continued 12 weeks of exposure after the last ustekinumab dose because of its long half life of approximately 3 weeks. The definitions also account for visit windows of 2 weeks. These definitions were agreed upon at the pre-BLA meeting (proposed by applicant). The Safety Update provided for an additional 6 months of follow-up, and data submitted in the update are generally discussed in Section 7.7.*

#### Baseline Characteristics of Study Population

Certain baseline characteristics of the study population have been discussed (see Section 6.1.2). Other baseline characteristics included that most subjects had received phototherapy (65% and mostly UVB), at least one conventional systemic therapy (55%; defined as PUVA, methotrexate, acitretin cyclosporine) and 43% had received another biologic. Comorbidities at baseline included hypertension (27%), hyperlipidemia (20%), diabetes (11%), ischemic heart disease/coronary artery disease (4%).

**Baseline Demographics (Modified from Appendix B.2 ISS)**

	C0379T04	PHOENIX 1	PHOENIX 2	Combined Studies
Subjects randomized at Week 0	320	766	1230	2316
<b>Sex</b>				
n	320	766	1230	2316
Male	222 (69.4%)	531 (69.3%)	840 (68.3%)	1593 (68.8%)
Female	98 (30.6%)	235 (30.7%)	390 (31.7%)	723 (31.2%)
<b>Race</b>				
n	320	766	1230	2316
Caucasian	297 (92.8%)	717 (93.6%)	1128 (91.7%)	2142 (92.5%)
Black	6 (1.9%)	14 (1.8%)	27 (2.2%)	47 (2.0%)
Asian	10 (3.1%)	20 (2.6%)	50 (4.1%)	80 (3.5%)
Other	7 (2.2%)	15 (2.0%)	25 (2.0%)	47 (2.0%)
<b>Age (yrs)</b>				
n	320	766	1230	2316
Mean ± SD	44.9 ± 13.19	45.3 ± 11.71	46.2 ± 12.24	45.7 ± 12.21
Median	45.0	45.5	47.0	46.0
IQ range	(35.0, 54.0)	(37.0, 53.0)	(38.0, 55.0)	(37.0, 55.0)
Range	(18, 79)	(19, 76)	(18, 86)	(18, 86)
<b>Weight (kg)</b>				
n	320	766	1229	2315
Mean ± SD	92.96 ± 22.744	93.88 ± 23.685	90.99 ± 21.278	92.22 ± 22.334
Median	89.00	91.60	88.60	89.80
IQ range	(77.25, 105.65)	(76.80, 107.50)	(76.00, 103.80)	(76.80, 105.00)
Range	(51.0, 220.4)	(46.9, 183.2)	(37.4, 195.1)	(37.4, 220.4)
<b>Height (cm)</b>				
n	319	766	1230	2315
Mean ± SD	171.8 ± 9.89	172.0 ± 10.05	172.2 ± 9.61	172.1 ± 9.79
Median	172.0	173.0	173.0	173.0
IQ range	(165.0, 179.0)	(165.0, 179.0)	(165.0, 179.0)	(165.0, 179.0)
Range	(141, 191)	(132, 201)	(138, 201)	(132, 201)
<b>BMI</b>				
n	319	766	1229	2314
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 (≥ 30)	149 (46.7%)	386 (50.4%)	594 (48.3%)	1129 (48.8%)

**Baseline Disease Characteristics**

Source: Appendix B.3 of ISS  
 Combined Studies

	C0379T04	PHOENIX 1	PHOENIX 2	Combined Studies
Subjects randomized at Week 0	320	766	1230	2316
<b>Psoriasis disease duration (yrs)</b>				
n	320	766	1230	2316
Mean ± SD	18.21 ± 12.060	19.92 ± 11.460	20.12 ± 12.074	19.79 ± 11.885
Median	16.10	18.33	18.53	18.23
IQ range	(9.10, 24.10)	(11.16, 28.16)	(10.41, 27.61)	(10.35, 27.54)
Range	(0.6, 61.0)	(0.6, 58.1)	(0.5, 64.4)	(0.5, 64.4)
<b>Age at diagnosis (yrs)</b>				
n	320	766	1230	2316
Mean ± SD	26.8 ± 14.00	25.4 ± 13.15	26.2 ± 13.64	26.0 ± 13.53
Median	24.5	23.0	24.0	24.0
IQ range	(16.0, 38.0)	(16.0, 34.0)	(16.0, 35.0)	(16.0, 35.0)
Range	(0, 71)	(0, 74)	(0, 85)	(0, 85)
<b>BSA (%)</b>				
n	319	766	1230	2315
Mean ± SD	27.2 ± 17.45	26.7 ± 16.70	26.4 ± 16.81	26.6 ± 16.86
Median	21.0	21.0	20.0	21.0
IQ range	(15.0, 33.0)	(15.0, 33.0)	(14.0, 32.0)	(15.0, 33.0)
Range	(10, 92)	(10, 96)	(10, 98)	(10, 98)
<b>BSA</b>				
n	319	766	1230	2315
≥ 20%	181 (56.7%)	421 (55.0%)	662 (53.8%)	1264 (54.6%)
<b>Psoriatic arthritis</b>				
n	320	766	1230	2316
Yes	62 (19.4%)	258 (33.7%)	305 (24.8%)	625 (27.0%)
No	258 (80.6%)	508 (66.3%)	925 (75.2%)	1691 (73.0%)
<b>PASI score (0-72)</b>				
n	320	766	1230	2316
Mean ± SD	19.12 ± 7.568	20.22 ± 8.287	19.61 ± 7.265	19.75 ± 7.664
Median	16.40	17.60	17.50	17.40
IQ range	(13.80, 21.80)	(14.50, 22.60)	(14.40, 22.50)	(14.40, 22.40)
Range	(12.0, 51.0)	(12.0, 62.0)	(12.0, 60.6)	(12.0, 62.0)

(continued on next page)

	C0379T04	PHOENIX 1	PHOENIX 2	Combined Studies
<b>PASI score</b>				
n	320	766	1230	2316
≥ 20	97 (30.3%)	260 (33.9%)	433 (35.2%)	790 (34.1%)
<b>PGA score<sup>a</sup></b>				
n	NA	765	1230	1995
Mild (2)	NA	42 (5.5%)	96 (7.8%)	138 (6.9%)
Moderate (3)	NA	388 (50.7%)	646 (52.5%)	1034 (51.8%)
Marked (4)	NA	298 (39.0%)	424 (34.5%)	722 (36.2%)
Severe (5)	NA	37 (4.8%)	64 (5.2%)	101 (5.1%)
<b>PGA score<sup>a</sup></b>				
n	NA	765	1230	1995
Marked or severe (≥ 4)	NA	335 (43.8%)	488 (39.7%)	823 (41.3%)

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

Summary of psoriasis medication history; subjects randomized at Week 0 in psoriasis Phase 2 and Phase 3 (Appendix B.4 ISS)

	C0379T04 <sup>a</sup>	PHOENIX 1	PHOENIX 2	Cominea Studies
Subjects randomized at Week 0	320	766	1230	2316
Treatment received				
Topical				
n	320	766	1230	2316
Never used	14 (4.4%)	40 (5.2%)	57 (4.6%)	111 (4.8%)
Ever used	306 (95.6%)	726 (94.8%)	1173 (95.4%)	2205 (95.2%)
UVB				
n	320	766	1230	2316
Never used	176 (55.0%)	342 (44.6%)	509 (41.4%)	1027 (44.3%)
Ever used	144 (45.0%)	424 (55.4%)	721 (58.6%)	1289 (55.7%)
PUVA				
n	320	766	1230	2316
Never used	234 (73.1%)	571 (74.5%)	886 (72.0%)	1691 (73.0%)
Ever used	86 (26.9%)	195 (25.5%)	344 (28.0%)	625 (27.0%)
Phototherapy (UVB or PUVA)				
n	320	766	1230	2316
Never used	134 (41.9%)	274 (35.8%)	401 (32.6%)	809 (34.9%)
Ever used	186 (58.1%)	492 (64.2%)	829 (67.4%)	1507 (65.1%)
Methotrexate				
n	320	766	1230	2316
Never used	233 (72.8%)	488 (63.7%)	804 (65.4%)	1525 (65.8%)
Ever used	87 (27.2%)	278 (36.3%)	426 (34.6%)	791 (34.2%)
Acitretin				
n	320	766	1230	2316
Never used	272 (85.0%)	639 (83.4%)	1007 (81.9%)	1918 (82.8%)
Ever used	48 (15.0%)	127 (16.6%)	223 (18.1%)	398 (17.2%)
Cyclosporine				
n	320	766	1230	2316
Never used	281 (87.8%)	654 (85.4%)	1067 (86.7%)	2002 (86.4%)
Ever used	39 (12.2%)	112 (14.6%)	163 (13.3%)	314 (13.6%)
Conventional systemics (PUVA, methotrexate, acitretin, cyclosporine)				
n	320	766	1230	2316
≥ 1 therapy	161 (50.3%)	424 (55.4%)	688 (55.9%)	1273 (55.0%)
≥ 2 therapies	65 (20.3%)	203 (26.5%)	317 (25.8%)	585 (25.3%)
≥ 3 therapies	26 (8.1%)	71 (9.3%)	119 (9.7%)	216 (9.3%)

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

Biologics (etanercept, alefacept, efalizumab, infliximab, adalimumab)				
n	NA	766	1230	1996
Never used	NA	374 (48.8%)	764 (62.1%)	1138 (57.0%)
Ever used	NA	392 (51.2%)	466 (37.9%)	858 (43.0%)
Conventional systemics or biologics				
n	NA	766	1230	1996
Never used	NA	213 (27.8%)	407 (33.1%)	620 (31.1%)
Ever used	NA	553 (72.2%)	823 (66.9%)	1376 (68.9%)

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

**Appendix B.7 Summary of medical history and current diagnoses; subjects randomized at Week 0 in psoriasis Phase 2 and Phase 3**

	C0379T04*	PHOENIX 1	PHOENIX 2	Combined Studies
Subjects randomized at Week 0	320	766	1230	2316
Diabetes mellitus	38 (11.9%)	91 (11.9%)	125 (10.2%)	254 (11.0%)
Requiring insulin	NA	11 (1.4%)	24 (2.0%)	35 (1.8%)
Hyperlipidemia	48 (15.0%)	170 (22.2%)	253 (20.6%)	471 (20.3%)
Requiring therapy	NA	115 (15.0%)	160 (13.0%)	275 (13.8%)
Hypertension	78 (24.4%)	218 (28.5%)	337 (27.4%)	633 (27.3%)
Requiring therapy	NA	174 (22.7%)	277 (22.5%)	451 (22.6%)
Family history of early coronary artery disease (< 55 years of age)	NA	101 (13.2%)	132 (10.7%)	233 (11.7%)
Ischemic heart disease/ coronary artery disease	12 (3.8%)	25 (3.3%)	51 (4.1%)	88 (3.8%)
Myocardial infarction	NA	9 (1.2%)	25 (2.0%)	34 (1.7%)
Angina pectoris	NA	7 (0.9%)	6 (0.5%)	13 (0.7%)
Coronary artery bypass graft	NA	7 (0.9%)	15 (1.2%)	22 (1.1%)
Percutaneous coronary intervention	NA	5 (0.7%)	15 (1.2%)	20 (1.0%)
Other	NA	5 (0.7%)	13 (1.1%)	18 (0.9%)
Congestive heart failure	NA	1 (0.1%)	3 (0.2%)	4 (0.2%)
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%)
Asthma	NA	68 (8.9%)	92 (7.5%)	160 (8.0%)
Seasonal allergy/hayfever	NA	194 (25.3%)	256 (20.8%)	450 (22.5%)
Chronic lung disease	NA	14 (1.8%)	20 (1.6%)	34 (1.7%)
Atopic dermatitis	NA	6 (0.8%)	17 (1.4%)	23 (1.2%)
Cirrhosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Liver fibrosis	1 (0.3%)	3 (0.4%)	4 (0.3%)	8 (0.3%)
Psoriatic arthritis	62 (19.4%)	258 (33.7%)	305 (24.8%)	625 (27.0%)

(continued on next page)

	CGS7104	PROELIX 1	PROELIX 2	Studies
Hospitalized within past 1 year (excluding pregnancy)	NA	27 (3.5%)	71 (5.8%)	98 (4.9%)
Hospitalized for an infection	NA	34 (4.4%)	69 (5.6%)	103 (5.2%)
Within past 1 year	NA	6 (0.8%)	15 (1.2%)	21 (1.1%)
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%)
Smoking (past or current)	NA	452 (59.0%)	777 (63.2%)	1229 (61.6%)
Still smoking	NA	242 (31.6%)	395 (32.1%)	637 (31.9%)
Stopped ≤ 1 year ago	NA	19 (2.5%)	40 (3.3%)	59 (3.0%)
Stopped > 1 year ago and ≤ 5 years ago	NA	36 (4.7%)	72 (5.9%)	108 (5.4%)
Stopped > 5 years ago and ≤ 10 years ago	NA	45 (5.9%)	75 (6.1%)	120 (6.0%)
Stopped > 10 years ago	NA	110 (14.4%)	194 (15.8%)	304 (15.2%)

\* NA = Not collected in Phase 2 study

*Comment: Demographic characteristics and comorbidities are consistent with what has been reported about psoriasis patients. Treatment groups were similar in demographic and disease characteristics and medical history.*

## 7.2.2 Explorations for Dose Response

The data presentations will generally be by treatment group, e.g. 45 mg, 90 mg. (See Section 7.1)

## 7.2.3 Special Animal and/or In Vitro Testing

The reader is referred to Sections 4.1 (Chemistry Manufacturing and Controls) 4.3. (Preclinical Pharmacology/Toxicology) and 4.4 (Clinical Pharmacology).

## 7.2.4 Routine Clinical Testing

Routine laboratory testing (hematology and chemistry) was done in the Phase 2 and 3 studies. Additional laboratory testing in Phase 3 included:

- C-reactive protein (as a surrogate marker of cardiovascular risk)
- D-dimer (as a surrogate marker of occult thrombosis)
- Hemoglobin A1c (to evaluate the impact of ustekinumab on glucose homeostasis)
- fasting glucose (to evaluate the impact of ustekinumab on diabetes)
- antibodies to ustekinumab (to evaluate immunogenicity potential)

The following testing was done only in Phase 1 and/or Phase 2 studies:

- Subsets of lymphocytes to determine the impact of ustekinumab on numbers and distribution of circulating lymphocytes

- Electrocardiograms (ECGs)
- Immune responses to vaccines were examined in the Phase 1 studies to assess immunocompetency

*Comment: Routine clinical testing was generally acceptable.*

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

The applicant states in Section 3.3 of the Summary of Clinical Pharmacology submitted in the licensing application:

“The exact metabolic pathway for CNTO 1275 has not been characterized. As a fully human IgG1κ mAb, CNTO 1275 is expected to be metabolized in the same manner as any other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), and is subject to similar elimination...Renal excretion and hepatic enzyme-mediated metabolism are therefore unlikely to represent major elimination routes. As such, variations in renal and hepatic function are not expected to affect the elimination of CNTO 1275.”

The applicant did not perform drug-drug interaction studies (see Section 7.5.5).

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no marketed products in this class; the product is a first-in-class monoclonal antibody.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

Four deaths were reported in the clinical development program:

#### Subject C0743T09-122-023

This subject was a 33-year-old Caucasian male who received ustekinumab 90 mg on August 3 and 31, 2006. On \_\_\_\_\_, he was found dead in bed. His parents reported that he had no complaints through the day of death.

His past medical history included hyperlipidemia, hypertension, seizure disorder, Graves' disease, family history of early-onset heart disease (his grandfather suffered his 1st heart attack while in his 30s). His BMI was 37.6. He had been without seizures and antiepileptics for > 4 years. He was hospitalized in \_\_\_\_\_ because of breathing difficulty and disorientation. No evidence of seizure activity was found.

Autopsy findings included cardiomegaly and no evidence of significant atherosclerosis. The autopsy report noted the cause of death as sudden cardiac death due to dilated cardiomyopathy, and hypertension was noted as a contributing factor. The manner of death was natural. The toxicology report was negative.

**b(6)**

*Comment: It is possible that his obesity and thyroid disease may have had some contributory role for his cardiomyopathy. Given the autopsy findings, the reviewer does not consider it likely that death was related to study agent.*

**Subject C0743T09 404-030**

This subject was a 63-year-old Caucasian male who received ustekinumab 45 mg on November 8, 2006 and December 6, February 27, and May 24, 2007. He was found dead in his home on [REDACTED]. The exact date of death was unknown (although it was sometime on or after [REDACTED], as he received a dose of placebo on this date). His past medical history included hypertension, alcohol use, liver enzyme abnormalities, and cigarette smoking.

Autopsy findings included advanced decomposition of the corpse with autolysis, fatty degeneration of the liver, arteriosclerosis of the kidneys, atherosclerosis of large body vessels, previous rib fractures, and aspiration of vomit. A suitable blood specimen could not be obtained. No cause of death was confirmed due to the extent of putrefaction; however, based on the toxicology report on urine and stomach contents, alcohol poisoning could not be excluded as a cause of death. The investigator believed that alcohol intoxication, vomiting and aspiration of vomited material likely caused the death of the subject.

*Comment: The reviewer believes the investigator presents a reasonable scenario.*

**Subject C0743T09 118-031**

This subject was 42-year old Caucasian female who received ustekinumab 90 mg on June 2, July 3, September 22, December 18, 2006, and February 12, April 10 and July 31, 2007. Her medical history included endometriosis, hiatal hernia, gastroesophageal reflux disease, obesity, smoking (1996-1998), tubal ligation, abnormal Pap smear, ovarian cyst, abnormal vaginal bleeding, petit mal seizures (vague history), irritable bowel syndrome and non-insulin dependent diabetes mellitus. Previous treatment for her psoriasis included etanercept, infliximab and adalimumab.

She was admitted to the hospital on [REDACTED] and underwent a pelvic laparotomy, elective total abdominal hysterectomy (for endometriosis), bilateral salpingo-oophorectomy, and umbilical hernia repair. No intraoperative complications were reported, estimated blood loss was 300 mL, and she was transferred to the recovery room in satisfactory condition.

She was reported to be hypotensive most of that day [REDACTED] with systolic blood pressure in the 60s and 70s, and the hypotension was thought to have been related to the morphine epidural she received during surgery. Her hemoglobin was 10.0 g/dL (was 13.7 g/dL the day prior). She was lethargic and had a brief syncopal episode of < one minute. She was resuscitated with intravenous fluids, given naloxone, and became more alert. At that time, there was no evidence of bleeding and she was moved to the step-down unit.

The following morning [REDACTED], she had a bradycardic event and emergency medical treatment was initiated. She went into full cardiac arrest, advanced cardiopulmonary life support was performed, and she was resuscitated after 40 minutes. She was transferred to the critical care unit. Her hemoglobin was 3.4 g/dL. She received 8 units of red blood cells and multiple units of fresh frozen plasma. Findings from an abdominal and pelvic computed tomography done [REDACTED] included "hyperdense fluid consistent with blood within the lower abdomen and extending through the pelvis." She was thought to have suffered massive intra-abdominal

hemorrhage which led to hemorrhagic shock and cardiopulmonary arrest. Over the next 36 hours, she developed multi-organ failure and disseminated intravascular coagulation. Results of a CT scan of the head done on \_\_\_\_\_ and her minimal responsiveness were both consistent with anoxic brain injury. She was unresponsive to voice or deep painful stimulus. Pupils were fixed at 5 mm without corneal reflex, and gag reflex was absent. She continued to deteriorate and died on \_\_\_\_\_ /.

b(6)

Autopsy findings included cardiomegaly with biventricular hypertrophy and dilatation, pulmonary edema, hemoperitoneum. There were 1700 cc of fresh blood and coagulum in the abdomen and pelvis and 150 cc of serosanguinous fluid in the chest cavity. No source for the hemorrhage was identified. She was also found to have papillary thyroid cancer (which was not clinically evident) with lymphocytic thyroiditis.

*Comment: This subject obviously had a very complicated and tragic postoperative course, which would not appear to have been related to ustekinumab. The hemorrhagic event may have begun very early in the postoperative period, given the hypotension and observed drop in hematocrit as compared to that the day prior to surgery. It is noted too that she was found to have a subclinical thyroid cancer. However, the extent (if any) to which this might have been related to ustekinumab exposure is unclear, since she had also been treated with 3 other biologics for her psoriasis (etanercept, infliximab and adalimumab).*

#### **Subject T09-019-042: metastatic kidney cancer**

This subject was a 66 y/o male who received ustekinumab 90 mg on October 23, November 20, 2006, and February 26, May 7, 2007, and a 5<sup>th</sup> dose approximately 180 days later (on Day 461) date not provided. On \_\_\_\_\_ metastatic kidney cancer was reported. He had experienced flank pain and hematuria for an unspecified period and had been treated with oral antibiotics presumptively for a urinary tract infection. Failing treatment, he underwent a renal ultrasound. He was found to have an inoperable kidney tumor with hepatic metastasis. Biopsy was not performed. He was advised that he was not a candidate for systemic therapy and was hospitalized for palliative care. He developed fever, mental status changes, hepatic and renal failure. He died on \_\_\_\_\_

b(6)

*Comment: This subject was included in the Safety Update. Relatedness to ustekinumab is possible.*

### 7.3.2 Nonfatal Serious Adverse Events

A total of 86 subjects experienced non-fatal serious adverse events (hereafter referred to simply as "serious adverse events"). Serious adverse events were most frequently reported in the "Cardiac disorders" and "Infections and infestations" system organ classes.

#### **Through Week 12**

Serious adverse events were reported for 34 subjects in the first 12 weeks (i.e. during the placebo-controlled period). The proportions of subjects who had at least one serious adverse were 1.4 % in the placebo group, 1.6% in the 45 mg group and 1.4% in the 90 mg group. Serious adverse events were most frequently reported in the "Cardiac disorders" and "Infections and infestations" system organ classes.

Cardiac disorders were reported in 0.0%, 0.1%, and 0.5% of subjects in the placebo, 45 mg, and 90 mg groups, respectively (single reports of each event). In the 45 mg group, the event was angina pectoris, and in the 90 mg group, the events were acute myocardial infarction, congestive cardiomyopathy, coronary artery disease, palpitations and ventricular extrasystoles. One serious cardiac event occurred in the placebo group 3 days after the Week 12 visit (further discussed later in the review).

Infections and infestations were reported in 0.4%, 0.0%, and 0.5% of subjects in the placebo, 45 mg, and 90 mg groups, respectively. In the placebo group the events were cellulitis (two reports) and pneumonia, and in the 90 mg group, the events were cellulitis (two reports), herpes zoster and pneumonia. There were no events reported in the "Infections and infestations" system organ class in the 45 mg group.

The one other serious adverse event for which there was more than more report was intervertebral disc protrusion (two subjects).

*Comment: The overall rates of serious adverse events were similar between treatment groups. The Phase 2 study generated concern regarding occurrence of occlusive vascular events in subjects treated with ustekinumab. Two such events (myocardial infarction and cerebrovascular event) occurred in ustekinumab-treated subjects in the Phase 2 study during the first 12 weeks (an additional MI occurred in this study after the 12-week time point and is captured in the presentation of serious adverse events that occurred through the end of the reporting period). In the Phase 2 study, randomization was 4:1 (301 ustekinumab: 64 placebo). The reviewer agrees with the applicant that the imbalance in randomization contribute to the challenges to making a determination of relatedness of these events to ustekinumab exposure (the affected subjects are discussed later in this review).*

The remainder of this page is left intentionally blank.

Number of subjects with 1 or more treatment-emergent serious adverse events through Week 12  
 Source: Table 8 of ISS

	Placebo	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 serious adverse events	10 (1.4%)	13 (1.6%)	11 (1.4%)	24 (1.5%)
<b>System-organ class/preferred term</b>				
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%)

(continued on next page)

	Placebo	45 mg	90 mg	Combined
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%)
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%)

#### Through the End of the Reporting Period

Serious adverse events were reported for a total of 86 subjects through the end of the reporting period. The proportions of subjects who had at least one serious adverse were 1.5 % in the placebo group, 3.1% in the placebo → 45 mg group, 1.6% in the placebo → 90 mg group, 4.1% in the 45 mg group and 3.4% in the 90 mg group. Again, serious adverse events were most frequently reported in the “Cardiac disorders” and “Infections and infestations” system organ classes.

*Comment: For the presentation of serious adverse events through the end of the reporting period, the reviewer elected to present certain serious adverse events by category to make the presentation more manageable for the review document (rather than inserting a single table that spans numerous pages). Additionally, select subjects within each category are described in narrative to provide additional detail. (Note: The reviewer attached the narratives to the presentation of events through the end of the reporting period as this period captures all of the events, i.e. the reporting through the end of the reporting period would include subjects whose events occurred in the placebo-controlled portion of the study).*

**Serious Cardiac Events**

Serious cardiac events were reported for 16 subjects:

**Serious Cardiovascular Events through the End of the Reporting Period** Source Appendix B.23 of ISS  
 CNTO 1375

	Placebo	Placebo → 45 mg	Placebo → 90 mg	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
Subjects with 1 or more serious adverse events	11 (1.5%)	10 (3.1%)	6 (1.6%)	32 (4.1%)	27 (3.4%)	75 (3.3%)
<b>System-organ class/preferred term</b>						
Cardiac disorders	1 (0.1%)	1 (0.3%)	1 (0.3%)	4 (0.5%)	9 (1.1%)	15 (0.7%)
Coronary artery disease	1 (0.1%)	0 (0.0%)	1 (0.3%)	1 (0.1%)	4 (0.5%)	6 (0.3%)
Myocardial infarction	1 (0.1%)	0 (0.0%)	1 (0.3%)	1 (0.1%)	1 (0.1%)	3 (0.1%)
Acute myocardial infarction	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
Angina pectoris	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Angina unstable	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Atrial fibrillation	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Cardiac failure congestive	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Congestive cardiomyopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Palpitations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Ventricular extrasystoles	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Ventricular tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)

The remainder of this page is left intentionally blank.

**Serious Cardiovascular Events per hundred subject-years of follow-up through the end of the reporting period**  
 Source Appendix B.24 of ISS

	Placebo	CNTO 1275				Combined
		Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg	
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
Number of serious adverse events per hundred subject-years of follow-up	8.78	9.24	3.97	6.58	6.89	6.68
<b>System-organ class/preferred term</b>						
Cardiac disorders	1.10	0.62	1.14	0.89	1.94	1.30
Coronary artery disease	0.55	0.00	0.57	0.18	0.71	0.41
Myocardial infarction	0.55	0.00	0.57	0.18	0.18	0.20
Acute myocardial infarction	0.00	0.00	0.00	0.18	0.18	0.14
Angina pectoris	0.00	0.00	0.00	0.18	0.00	0.07
Angina unstable	0.00	0.00	0.00	0.18	0.00	0.07
Atrial fibrillation	0.00	0.62	0.00	0.00	0.00	0.07
Cardiac failure congestive	0.00	0.00	0.00	0.00	0.18	0.07
Congestive cardiomyopathy	0.00	0.00	0.00	0.00	0.18	0.07
Palpitations	0.00	0.00	0.00	0.00	0.18	0.07
Ventricular extrasystoles	0.00	0.00	0.00	0.00	0.18	0.07
Ventricular tachycardia	0.00	0.00	0.00	0.00	0.18	0.07

*Comment: The proportion of subjects reported in the placebo group increases slightly, relative to what was reported through Week 12 because of a subject (Subject C0743T09-128-001) who had the serious adverse events of myocardial infarction (MI) and coronary artery disease (CAD) at Week 13. These events occurred 3 days after the Week 12 visit and therefore were not included in the Week 12 reporting. This subject had discontinued study agent after a single administration at Week 0 and was in the protocol-specified 20-week follow-up period performed for all subjects who discontinued study agent. When adjusted per hundred subject-years, the incidence of cardiac events was highest in the 90mg group. However, when all treatment groups are considered, in the reviewer's opinion, no pattern is evidenced to suggest an ustekinumab effect on the risk of serious cardiovascular events..*

Myocardial Infarctions

Six myocardial infarctions were reported through the end of the reporting period: one in the placebo group, 2 in the 45 mg group and 3 in the 90 mg group. The subjects are discussed below.

Subject T04-002-001

This was a 61 y/o male whose medical history included Type 2 diabetes and hypertension. His BMI was 30.0 (overweight). He received one dose of ustekinumab 90 mg, and that was on August 5, 2003. On \_\_\_\_\_, he was diagnosed with a myocardial infarction. A cardiac catheterization demonstrated severe multivessel coronary artery disease with 90 % proximal left anterior descending, severe circumflex disease up to 90 to 95 %, and a proximal right coronary artery stenosis of 70 to 80 %, with an ejection fraction of about 50 %. He underwent 5-vessel coronary artery bypass \_\_\_\_\_

b(6)

*Comment: This subject obviously had severe atherosclerotic disease which could not have developed in 4 month's time. His risk factors for MI include diabetes and hypertension. His BMI would categorize him as being at the threshold of obesity (BMI > 30 is obese). Given the extent of his disease, the reviewer considers any role for the single dose of ustekinumab to be doubtful.*

Subject T04-003-006

This was a 54 y/o male whose medical history included Type 2 diabetes and smoking. His BMI was 29.5 (overweight) He received his first dose of ustekinumab 90 mg on July 29, 2003. Approximately 1 hour later, his blood pressure was noted to have increased from 130/78 (?pre-injection) to 192/105 (his blood pressure at screening was 150/80). He received his 2<sup>nd</sup> dose of ustekinumab on August 5. Pre-injection blood pressure was 147/81; 15-minute post injection blood pressure was 148/83, and a 1-hour post injection blood pressure was 140/83.

On \_\_\_\_\_, he experienced a myocardial infarction. He presented to the emergency room on \_\_\_\_\_ of "chest uneasiness". Additionally, he experienced chest pain while working (with radiation to jaw) with associated diaphoresis and vomiting. Laboratory values showed a CK-MB level of 29.6, with a troponin I level of 18.6 (units and normal ranges unspecified). An ECG on admission was read as a "probable subacute MI." He underwent an emergency cardiac catheterization that same day with stenting in the right coronary artery. He was found to have tight lesions involving the left anterior descending and the second marginal branch of the circumflex system, with residual disease in the right system. He underwent 4-vessel coronary artery bypass graft surgery the following day \_\_\_\_\_. He was discharged on \_\_\_\_\_.

b(6)

b(6)

*Comment: This is a relatively young subject who had risk factors for cardiovascular disease/MI. He was found to have significant vessel disease and appears that he may have had hypertension. As with the previous subject, the extent of his vessel disease indicates that he was at risk for MI in the absence of exposure to study product.*

Subject T08-029-010

This subject was a 61 y/o male whose medical history included hyperlipidemia, ischemic heart/coronary artery disease, and cigarette smoking. His BMI was 31.6 (obese). He received ustekinumab 45 mg on March 9 (Week 0), April 11, June 29, September 21, and December 14, 2006.

On \_\_\_\_\_, he underwent nephrectomy for a malignant tumor of the left kidney (this subject is also discussed under Malignancies). That afternoon, he developed sudden onset of chest discomfort. An ECG revealed significant ST elevation in the anterior leads consistent with an acute anterior infarct. He underwent emergency left heart catheterization and selective coronary arteriography which revealed severe single vessel coronary artery disease manifested by acutely occluded proximal left anterior descending disease. Minor luminal irregularities were identified involving the body of the left circumflex and right coronary artery with a widely patent stent site in the distal left circumflex. He also underwent a percutaneous transluminal coronary angioplasty of the proximal left anterior descending coronary artery. A drug eluting stent was placed in the proximal left anterior descending coronary artery.

b(6)

**Comment:** *This subject may have been at heightened risk for post-operative MI because of his medical history (Note: He had been maintained on perioperative beta-blocker therapy.)*

Subject T08-100-021

This was a 66 y/o male whose medical history included hypertension and cigarette smoking. His BMI was 34.0 (obese). He received ustekinumab 90 mg on June 16 (Week 12), July 14 and November 1, 2006 (crossed over from placebo at Week 12).

On June 16, the adverse event of "worsening of hypertension" was recorded. On June 19, the adverse events of "dyspnea with effort" and "coronary artery disease" were recorded. On \_\_\_\_\_, he was diagnosed with MI and worsening coronary artery disease. Coronarography revealed coronary artery disease (specifics not provided). CK-MB level of 9.74 ng/mL (normal: 0.0-5.0 ng/mL) and a troponin level of 0.085 µg/L (normal: 0.000-0.030 µg/L). He underwent coronary artery bypass surgery. He received an additional (and final scheduled) dose of ustekinumab (November 1, 2006).

b(6)

**Comment:** *This subject also had risk factors for MI. It appears his cardiovascular status was becoming more unstable at initiation of ustekinumab treatment. It is noted too that the occurrence of MI did not preclude his receiving his last scheduled dose of ustekinumab. He completed his Week 48 visit with no additional reports of adverse events.*

Subject T08-107-029

This subject was a 61 y/o male whose medical history included hyperlipidemia, hypertension, ischemic heart/coronary artery disease, stroke, alcohol intake, and cigarette smoking. His BMI was 34.5 (obese). He received ustekinumab 45 mg on March 30 (Week 0), April 26, July 20, and October 12, 2006. On \_\_\_\_\_, he experienced a sudden onset of substernal pressure associated with diaphoresis. He syncopized and was found by emergency services to be in ventricular fibrillation. He was defibrillated and transferred to a hospital. Postresuscitation electrocardiogram showed normal sinus rhythm without evidence of ischemia or infarct. There was some early transition in the anterior leads and some diffuse nonspecific T-wave abnormalities. He was diagnosed with the serious adverse events of myocardial infarction and coronary artery disease on the same day. On September 2, his CK was 294 (normal 6-115), and his troponin level was 0.47 (normal < 0.031). He underwent a double cardiac bypass on \_\_\_\_\_. A carotid Doppler ultrasound on the same day revealed 16% to 49% stenosis of the left internal carotid artery and normal right carotid system. His postoperative course was uneventful. The subject was discharged from the hospital on \_\_\_\_\_. He received his 4<sup>th</sup> and last dose of ustekinumab on October 12, 2006.

b(6)

**Comment:** *It is noted that the subject received an additional dose of ustekinumab post MI and completed his Week 28 visit.*

Subject T09-128-001

The subject was a 59 y/o female whose medical history included hyperlipidemia, hypertension, and cigarette smoking. Her BMI was 27.7. The event occurred prior to receiving any ustekinumab (she was randomized to crossover to 90 mg, but did not). On Day 85, she experienced burning in her chest, nausea, vomiting, dizziness, and fatigue. ECG showed findings suggesting an inferoposterior infarct. Cardiac catheterization revealed left main and right coronary artery disease with acute inferoposterior myocardial infarction. Primary

b(6)

percutaneous coronary intervention of the right coronary artery with drug-eluting stenting was successful. She was discharged \_\_\_\_\_ and scheduled to return later in the month for coronary artery bypass graft (she underwent a triple bypass surgery).

b(6)

*Comment: This subject's MI occurred at approximately Month 3. In subjects who received ustekinumab, MIs occurred at approximately Week 2, Months 4, 5, 5.5 and 12. This suggests that the longer follow-up might have increased the possibility that certain adverse events (MI) might have been seen in subjects with risk factors and, perhaps, irrespective of exposure to study agent. (In fact, as a general principle, the longer the follow-up, the greater the possibility of an adverse event, e.g. skin laceration, rhinitis, headache, etc.) The reviewer identified no pattern in regard to occurrence of MI and exposure to ustekinumab (whether by dose group, 45 mg or 90 mg, or numbers of doses received). Additionally, 2 subjects received ustekinumab post MI without reports of other cardiac adverse events.*

*In the Phase 3 studies, any adverse event that occurred after Week 12 generally would reflect some amount of ustekinumab exposure, since all subjects who remained under treatment received ustekinumab beginning at Week 12 (because of cross-over study design). Also see Section 7.3.2.*

### Serious Infections

A total of 18 subjects reported serious infections, 15 of whom received treatment with ustekinumab.

#### Serious Infections through the End of the Reporting Period

Source Appendix B.23 of ISS

	Placebo	CNTO-1275				
		Placebo → 45 mg	Placebo → 90 mg	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
Subjects with 1 or more serious adverse events	11 (1.5%)	10 (3.1%)	6 (1.6%)	32 (4.1%)	27 (3.4%)	75 (3.3%)
<b>Infections and infestations</b>	<b>3 (0.4%)</b>	<b>1 (0.3%)</b>	<b>0 (0.0%)</b>	<b>3 (0.4%)</b>	<b>11 (1.4%)</b>	<b>15 (0.7%)</b>
Cellulitis	2 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	3 (0.4%)	4 (0.2%)
Diverticulitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	2 (0.1%)
Viral infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
Gastroenteritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Herpes zoster	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Meningitis aseptic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Osteomyelitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Pneumonia	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Sepsis	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Urinary tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Wound infection staphylococcal	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)

**Serious Infections per hundred subject-years of follow-up through the end of the reporting period**  
 Source Appendix B.24 of ISS

	Placebo	Placebo → 45 mg	Placebo → 90 mg	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
Number of serious adverse events per hundred subject-years of follow-up	8.78	9.24	3.97	6.58	6.89	6.68
Infections and infestations	1.65	1.23	0.00	0.53	1.94	1.09
Cellulitis	1.10	0.00	0.00	0.18	0.53	0.27
Diverticulitis	0.00	0.00	0.00	0.00	0.35	0.14
Viral infection	0.00	0.00	0.00	0.18	0.18	0.14
Gastroenteritis	0.00	0.00	0.00	0.00	0.18	0.07
Herpes zoster	0.00	0.00	0.00	0.00	0.18	0.07
Meningitis aseptic	0.00	0.00	0.00	0.00	0.18	0.07
Osteomyelitis	0.00	0.00	0.00	0.18	0.00	0.07
Pneumonia	0.55	0.00	0.00	0.00	0.18	0.07
Sepsis	0.00	0.62	0.00	0.00	0.00	0.07
Urinary tract infection	0.00	0.00	0.00	0.00	0.18	0.07
Wound infection staphylococcal	0.00	0.62	0.00	0.00	0.00	0.07

*Comment: Again, the highest incidence of serious infections per hundred-subjects was in the 90 mg group. However, the reviewer identified no pattern in regard to exposure to ustekinumab (whether by dose group, 45mg or 90 mg, or numbers of doses received) and occurrence of serious infections, e.g. no serious infections were reported in placebo → 90 mg group, and the incidence in the placebo group was > 3x that in the 45 mg group.*

Subject T04-015-018: cellulitis

This subject was a 22 y/o female with a 19-year history of psoriasis. She received an initial dose of ustekinumab 45 mg on December 22, 2003. On March 15, 84 days post initial dose (Day 85) she was noted to have an infection on the left ankle, which cultured *Staphylococcus aureus* and resolved following treatment with dicloxacillin.

She received a second dose of ustekinumab 45 mg on April 14, and \_\_\_\_\_ reported a constellation of signs and symptoms (including headache, neck stiffness, chills and “red patches” on legs) which led to emergency room referral and eventual admission to the intensive care unit with hypotension, renal insufficiency and hyponatremia. She was empirically started on broad-spectrum parenteral antibiotics. Urine cultures were significant for *Klebsiella pneumonia* (>100,000 Cfu/mL), and blood cultures obtained at admission were negative after > 96 hours. Lumbar puncture revealed no evidence of meningitis. Abdominal/pelvic CT scan revealed a 5 mm non-obstructing calculus in the left renal pelvis. MRI of the left leg showed reticular edema of the subcutaneous adipose tissue which extended into “the fascial planes between the soleus muscle and medial head of the gastrocnemius muscle with associated subtle edema of the musculature proper.” Infectious diseases experts considered her presentation to be most consistent with sepsis, a urinary tract infection, cellulitis, myositis, or a combination of these conditions.

Her hemodynamic and renal status improved during the first 3-5 days of admission. Persistent, significant left leg pain and edema made compartment syndrome a consideration. Intracompartmental pressures were found to be elevated, and she underwent a four-compartment

b(6)

Clinical Review  
Brenda Carr, M.D.  
BLA 125261  
Ustekinumab

fasciotomy. Drainage was serosanguinous, the muscle tissue appeared healthy, and there was no evidence of infection. Her pain was significantly relieved. She was ultimately discharged on \_\_\_\_\_ days post 2<sup>nd</sup> injection).

b(6)

*Comment: This subject is presented as she was young and had a somewhat complicated hospital course. The reviewer agrees that her presentation could have resulted from a combination of infectious events, and a contributory role for ustekinumab cannot be excluded.*

Subject T04-040-005: pneumonia

This subject was a 63 y/o Caucasian male who received his first dose of ustekinumab 90 mg on \_\_\_\_\_. The same day, he was noted to have an elevated white blood cell count of 12.6 (normal 4.1 to 12.3 x 10<sup>3</sup> uL, units not specified) and an elevated glucose of 429 (normal 68 to 169). The following day (Day 2), he was hospitalized with a severe pneumonia. He was treated with IV antibiotics (levofloxin), and the pneumonia was considered resolved on January 14, 2004 (Day 9).

b(6)

*Comment: A relatively elderly, diabetic received ustekinumab apparently in the face of an active "severe" pneumonia which responded well to treatment and he had an uneventful hospital course. He went on to receive 4 additional doses, including on Day 15, i.e. 6 days following resolution of the pneumonia. (Note: This subject also experienced a serious adverse event of cardiac failure on Day 185, 64 days after 5<sup>th</sup> dose.)*

Subject T-08-016-019: disseminated zoster

The 53 y/o female received one dose of ustekinumab 90 mg, and the date of that dose was January 19, 2006. She was reported to have experienced left flank pain on the day prior to dosing (recorded as an adverse event of back pain). On January 22 (Day 4; 3 days after dose), she was diagnosed with disseminated zoster. She reported a vesicular eruption began on her back, chest, and shoulder 2 or 3 days earlier. She exhibited vesicles in the left T-8 dermatome. The investigator counted all vesicles outside the left T-8 dermatomal distribution, a total of 19 vesicles in the following areas: right scalp (2), left arm (5), right arm (3), right lateral chest (6), right shoulder (2), and left leg (1). Tzanck smear from the breast and shoulder were positive. She was admitted for IV antiviral therapy on \_\_\_\_\_. There was no evidence of visceral involvement. She received IV acyclovir for 3 days, followed by oral valacyclovir. She was discharged on \_\_\_\_\_. Study agent was permanently discontinued.

b(6)

*Comment: A prodrome is suggested by the complaint of left flank pain prior to dosing with ustekinumab, and it appears that vesicles were erupting the day of or following initial dosing, suggesting no causative role for ustekinumab. While she had lesions outside of the T-8 dermatome and lesions that crossed the midline, the "dissemination" was of limited scope. She had an uncomplicated course and responded well to treatment.*

Subject T08-017-023: cellulitis

This subject was a 61 y/o male who received ustekinumab 90 mg on March 21, April 18, July 11, and October 11, 2006. His medical history included diabetes, hypertension and smoking. His primary care physician diagnosed cellulitis of the plantar aspect of the left foot on December 7, 2006 (Day 262; 57 days after the 4<sup>th</sup> and last dose of ustekinumab). The infection did not respond to oral antibiotics (amoxicillin/potassium clavulanate), the subject became febrile, and

he was admitted for IV treatment on [REDACTED]. He was discharged 2 days later [REDACTED] on oral antibiotics. He had a “well-healing”, crusted erosion on the plantar aspect of the left foot with surrounding residual edema and erythema. An MRI obtained on [REDACTED] (for reasons not specified) revealed an osteomyelitis of the left 5th digit with diffuse cellulitis; he also had an ulcer (?site). He was re-admitted and treated with IV antibiotics. The left 4<sup>th</sup> and 5<sup>th</sup> digits were amputated on [REDACTED]. He was discharged on [REDACTED] on a 10-day course of oral antibiotics (ciprofloxacin).

b(6)

*Comment: There are multiple factors which could have predisposed this elderly subject to ulcer and complications thereof (cellulitis, osteomyelitis) including his history of diabetes, hypertension and smoking. Relatedness to ustekinumab exposure to the course of events cannot be excluded. However, in the reviewer’s opinion, in a patient with this medical history, a similar clinical course might be followed in the absence of ustekinumab exposure.*

Subject T09-118-038: seroma; osteomyelitis

This subject was a 39 y/o male whose medical history included diabetes, diabetic neuropathy, peripheral vascular disease, and diabetic ulcers right lower extremity. He underwent right below-knee amputation (BKA) on [REDACTED] secondary to osteomyelitis.

b(6)

He received ustekinumab 45 mg on July 18 and August 16, 2006. On September 10 (Day 55; 25 days after 2<sup>nd</sup> dose), he was diagnosed with a seroma. On [REDACTED], he was admitted to the hospital with a BKA stump abscess. He was treated with intravenous antibiotics, and the abscess was drained on [REDACTED]. Wound cultures were negative, and he was afebrile. He refused his insulin. He was discharged on [REDACTED] and at his first post-discharge follow-up visit (September 21), the wound was said to have been healing well. The wound was assessed as showing continued improvement at on October 6 and as “well healed” on October 26, to the extent that he was going to be refitted for a prosthesis. The seroma was also assessed as resolved on this date. On November 24 (100 days after last dose of ustekinumab), the stump was reddened and showed a 1 cm breakdown, but no purulent drainage. He was seen in an emergency room on [REDACTED] and admitted the same day for “for suspicion of underlying infection and treated empirically with ertapenem. MRI done that day showed “osteomyelitis involving the distal 2 cm of the right tibial stump associated with extensive soft tissue involvement; no drainable collection was seen.” The subject was lost to follow-up.

*Comment: This is a young subject with complications from diabetes, suggesting perhaps a poor level of control over the years (it is noted too that he had refused insulin during a hospitalization). It is possible that ustekinumab could have contributed to a resurgence of a smoldering (chronic) osteomyelitis.*

Subject T09-200-002: cellulitis

This subject was a 42 y/o male who received ustekinumab 90 mg on June 23, July 21 and October 11, 2006. His medical history included diabetes. His BMI was 40.2 (obese). On August 9, the subject felt “sick” and had chills. The following day, [REDACTED] after 2<sup>nd</sup> dose), he noticed redness on his “underbelly.” He presented to the hospital with skin findings described as “extensive, partly raised, intensely red, and inflamed lesion corresponding to erysipelas on his abdomen.” He was diagnosed with cellulitis on the same day. He was treated with IV cefazolin, topical antiseptic and topical nystatin zinc oxide, which was said to

b(6)

have "improved the erysipelas." He was discharged on [REDACTED], and continued oral cephalexin through August 23. The event was assessed as resolve on August 21.

*Comment: Improvement could have been a function of the systemic antibiotics. However, the presenting skin findings and reported response to nystatin/zinc oxide also suggest intertrigo as a possibility in this obese subject. Intertriginous psoriasis might also be in the clinical differential diagnosis.*

Potential Opportunistic Infections

There were 5 reports of potential opportunistic infections (none serious): one report of oral thrust and 4 reports of herpes zoster.

Serious Nervous System Disorders

The rates of serious nervous system disorders were similar between treatment groups, occurring in < 1% of subjects in each group. Three subjects had cerebrovascular accidents (CVA), and all were in ustekinumab groups.

Serious Nervous System Disorders through the End of the Reporting Period Source Appendix B.23 of ISS  
 CNTO 1275

	Placebo	Placebo → 45 mg	Placebo → 90 mg	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
Subjects with 1 or more serious adverse events	11 (1.5%)	10 (3.1%)	5 (1.6%)	32 (4.1%)	27 (3.4%)	75 (3.3%)
Nervous system disorders	1 (0.1%)	2 (0.6%)	1 (0.3%)	4 (0.5%)	1 (0.1%)	8 (0.4%)
Cerebrovascular accident	0 (0.0%)	1 (0.3%)	0 (0.0%)	2 (0.3%)	0 (0.0%)	3 (0.1%)
Chorea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Dizziness	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Facial paresis	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Sciatica	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Cervicobrachial syndrome	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Serious Nervous System Disorders per hundred subject-years of follow-up through the End of the Reporting Period Source Appendix B.24 of ISS

	Placebo	Placebo → 45 mg	Placebo → 90 mg	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
Number of serious adverse events per hundred subject-years of follow-up	8.78	9.24	3.97	6.58	6.89	6.68

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

Nervous system disorders	0.55	1.23	0.57	0.71	0.18	0.55
Cerebrovascular accident	0.00	0.62	0.00	0.36	0.00	0.20
Chorea	0.00	0.00	0.00	0.00	0.18	0.07
Dizziness	0.00	0.00	0.57	0.00	0.00	0.07
Facial paresis	0.00	0.62	0.00	0.00	0.00	0.07
Headache	0.00	0.00	0.00	0.18	0.00	0.07
Sciatica	0.00	0.00	0.00	0.18	0.00	0.07
Cervicobrachial syndrome	0.55	0.00	0.00	0.00	0.00	0.00

Cerebrovascular Accidents (Also see Section 7.3.2)

Subject T04-015-019

This subject was a 59 y/o female whose medical history included hyperlipidemia and hypertension. She received ustekinumab 45 mg on January 19, 2004 (Day 1) and 3 subsequent doses on Days 10, 15, and 23.

On \_\_\_\_\_, she was diagnosed with a cerebrovascular accident (CVA). She experienced right-sided numbness and an inability to speak for which she apparently presented to the emergency room. She reported episodes ("spells"), which included numbness, over approximately the previous year. These episodes were less "dense" and cleared after several minutes. She experienced improvement in her leg and ability to speak in the emergency room. She also experienced substernal chest tightness for a week and an ECG showed some flattening of T waves in the anterior leads.

b(6)

A CT scan of the brain without contrast was normal, with moderate cerebral atrophy. A left-sided carotid duplex revealed evidence of hemodynamically significant internal carotid artery disease. The common carotid artery had a minimal to mild diameter reduction. Findings on MRI of the brain included multiple, small, acute lacunar-type infarctions in the left cerebrum involving the frontal, parietal, temporal, and occipital regions. The imaging pattern suggested an embolic source with the left carotid artery a possibility. Two small cortical infarcts in the left frontal lobe had a subacute to chronic MRI appearance.

On \_\_\_\_\_, she was diagnosed with severe carotid artery stenosis (she underwent diagnostic arteriogram). On May 12, 2004 (Day 115; 92 days after last dose), laboratory values included large platelets (normal: not present), a platelet count of 540,000 x 10<sup>3</sup> mL (normal: 140,000 x 10<sup>3</sup> mL to 540,000 x 10<sup>3</sup> mL), with +1 smudge cells (normal: not present), and +1 toxic granules (normal: not present). She was diagnosed with thrombocytosis. On \_\_\_\_\_ she underwent a left carotid endarterectomy with a patch angiography and intra-operative duplex, due to her left carotid stenosis.

b(6)

*Comment: Her history suggests possible transient ischemic attacks over the year prior to dosing with study agent. Her vessel disease placed her at risk for a CVA. The thrombocytosis may have been contributory to neurologic events.*

Subject T08-030-005

This subject was a 55 y/o male whose medical history included hyperlipidemia, ischemic heart/coronary artery disease, CABG (5 grafts), and hypertension. He received ustekinumab 45 mg (crossover from placebo at Week 12) on June 12, July 19 and October 9, 2006. On \_\_\_\_\_, he experienced right-sided weakness. He was admitted to the hospital the same day and diagnosed with a CVA. He reported headaches and spontaneously resolving right-sided weakness for 3 to 4 weeks prior to admission (recorded as adverse events on July 1,

b(6)

Clinical Review  
Brenda Carr, M.D.  
BLA 125261  
Ustekinumab

19 days after 1<sup>st</sup> injection). MRI findings were consistent with acute infarct of the left temporal and left basal ganglion regions that appeared more hypertensive in nature; however, a dissolved clot in the middle cerebellar artery distribution could not be ruled out. A follow-up CT on \_\_\_\_\_ (initial scan showed no acute pathology) found areas of low-density attenuation present in the left parietal operculum and left internal capsule, suggesting an acute process. Thrombophilia workup was negative. He improved with heparin, and was discharged on \_\_\_\_\_. He received one additional dose of ustekinumab 45 mg on October 9, 2006, and was followed-up through March 14, 2007.

b(6)

*Comment: This subject was at risk for a CVA. The reviewer does not see an obvious role for causation by ustekinumab in this event.*

Subject T08-030-009

This subject was a 65 y/o male whose medical history included borderline hypertension, sleep apnea, cigarette smoking (2 packs per day). His BMI was 40.9 (obese). He received ustekinumab 45 mg on March 13, April 10 and July 10, 2006. On \_\_\_\_\_ (2<sup>nd</sup> dose) he was diagnosed with a CVA. He was also diagnosed with hypertension. He had presented with right-sided weakness and slurred speech. He reported experiencing similar symptoms 4 days prior to admission/diagnosis. His blood pressure was 196/110 on admission. CT scan findings included a large area of low density in the right cerebellum with a suggestion of a slight mass effect, and these findings were thought to represent a subacute ischemic infarct, but a mass could not be excluded. Small low density areas were noted in the left parietal region that were thought to represent areas of ischemic injury. MRI scans revealed an area of recent nonhemorrhagic infarction involving the distribution of the right posterior inferior cerebellar artery and scattered chronic small vessel ischemic changes of periventricular white matter. Additional diagnoses included bilateral popliteal aneurysms (from workup for leg pain) and a mild aneurysmal dilation of the abdominal aorta. He was discharged on \_\_\_\_\_. He received a 3<sup>rd</sup> dose of ustekinumab on July 10, 2006, but was discontinued from the study thereafter.

b(6)

*Comment: This subject received an additional dose of ustekinumab following his CVA and there were no additional reports of adverse events.*

Subject T08-201-004: chorea

This was a 71 y/o F who received ustekinumab 90 mg on April 3, 2006 (Day 1) and May 2, 2006 (Day 30). On \_\_\_\_\_, she was diagnosed with chorea (choreiform movements, left side of body); however, her symptoms were initially reported on July 24. The movements were described as a "grabbing-like motion of the left hand and spasms in the left shoulder." She was also noted to have an. Other neurologic complaints included gait disturbances (unstable gait was observed) with "an impression of a scooting walk to the right" and an inclination to fall to the left for the past several months, involuntary movements of the left arm for days, a balance impairment for more than 1 year. Her mental functions were normal. Work-up included a CT scan of the brain on \_\_\_\_\_ and an MRI scan of the brain on \_\_\_\_\_. \_\_\_\_\_ were unremarkable except for cortical atrophy, consistent with age, and evidence of old ischemic lesions. The neurologist diagnosed pronounced axial dyskinesia in the 4 extremities, most pronounced in the left upper extremity, of undetermined cause. She was begun on amantadine discharged to home on \_\_\_\_\_. Follow-up visit on January 15, 2007

b(6)

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

revealed some remaining orofacial dyskinesia; amantadine was discontinued as dyskinesia had nearly resolved.

*Comment: This subject is presented as no etiology was determined for her neurologic events, and the chorea was considered possibly related to study agent. However, it is noted that she appears to have had some neurologic symptoms prior to study treatment.*

**Serious Gastrointestinal Disorders**

Serious Gastrointestinal Disorders through the end of the reporting period Source Appendix B.23 of ISS

	CNTO 1275					
	Placebo	Placebo → 45 mg	Placebo → 90 mg	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
Subjects with 1 or more serious adverse events	11 (1.5%)	10 (3.1%)	6 (1.6%)	32 (4.1%)	27 (3.4%)	75 (3.3%)
Gastrointestinal disorders	1 (0.1%)	2 (0.6%)	0 (0.0%)	2 (0.3%)	3 (0.4%)	7 (0.3%)
Abdominal hernia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Abdominal hernia obstructive	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Abdominal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Abdominal pain upper	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Appendicitis perforated	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Colitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Diverticular perforation	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Peritonitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Ascites	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Serious Gastrointestinal Disorders per hundred subject-years of follow-up through the End of the Reporting Period Source Appendix B.24 of ISS

	Placebo	Placebo → 45 mg	Placebo → 90 mg	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
Number of serious adverse events per hundred subject-years of follow-up	8.78	9.24	3.97	6.58	6.89	6.68
Gastrointestinal disorders	0.55	1.23	0.00	0.53	0.53	0.55
Abdominal hernia	0.00	0.00	0.00	0.00	0.18	0.07
Abdominal hernia obstructive	0.00	0.00	0.00	0.18	0.00	0.07
Abdominal pain	0.00	0.00	0.00	0.18	0.00	0.07
Abdominal pain upper	0.00	0.00	0.00	0.18	0.00	0.07
Appendicitis perforated	0.00	0.62	0.00	0.00	0.00	0.07
Colitis	0.00	0.00	0.00	0.00	0.18	0.07
Diverticular perforation	0.00	0.62	0.00	0.00	0.00	0.07
Peritonitis	0.00	0.00	0.00	0.00	0.18	0.07
Ascites	0.55	0.00	0.00	0.00	0.00	0.00

Subject T-08-003-003

This subject was a 44 y/o female who received ustekinumab 90 mg on March 1, April 5, June 21, and September 20, 2006. On \_\_\_\_\_ she was

b(6)

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

diagnosed with gastroenteritis. She was hospitalized the following day with complaints of nausea, vomiting, constipation, and abdominal pain (working diagnosis was small bowel obstruction). She developed diarrhea during the hospitalization. A white blood count was 8.3 (timepoint and normal range not provided). She was discharged on \_\_\_\_\_

b(6)

*Comment: This was the only serious adverse event of gastroenteritis, and it occurred approximately 6 months after her last dose of ustekinumab. Salmonellosis is not suggested by the history (although the provided history is somewhat vague).*

### Serious Neoplasms

Serious Neoplasms through the End of the Reporting Period Source Appendix B.23 of ISS

	Placebo	CNTO 1275				Combined
		Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg	
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
Subjects with 1 or more serious adverse events	11 (1.5%)	10 (3.1%)	6 (1.6%)	32 (4.1%)	27 (3.4%)	75 (3.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1%)	0 (0.0%)	0 (0.0%)	4 (0.5%)	2 (0.3%)	6 (0.3%)
Breast cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Meningioma benign	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Neoplasm malignant	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Prostate cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Thyroid gland cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Uterine leiomyoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Hepatic neoplasm malignant	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Serious Neoplasms per hundred subject-years of follow-up through the end of the reporting period  
 Source Appendix B.24 of ISS

	Placebo	Placebo → 45 mg	Placebo → 90 mg	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
Number of serious adverse events per hundred subject-years of follow-up	8.78	9.24	3.97	6.58	6.89	6.68
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0.55	0.00	0.00	0.71	0.35	0.41
Breast cancer	0.00	0.00	0.00	0.18	0.00	0.07
Meningioma benign	0.00	0.00	0.00	0.00	0.18	0.07
Neoplasm malignant	0.00	0.00	0.00	0.18	0.00	0.07
Prostate cancer	0.00	0.00	0.00	0.18	0.00	0.07
Thyroid gland cancer	0.00	0.00	0.00	0.18	0.00	0.07
Uterine leiomyoma	0.00	0.00	0.00	0.00	0.18	0.07
Hepatic neoplasm malignant	0.55	0.00	0.00	0.00	0.00	0.00

*Comment: The data above do not suggest a correlation between the occurrence of serious malignancies and ustekinumab exposure.*

Subject T04-022-004 : prostate adenocarcinoma

The subject was a 64 y/o male who received one dose of ustekinumab 45 mg on January 13, 2004. He was found to have an elevated prostate-specific antigen (PSA) of 5.7 ng/mL 7 days later (normal: 0.0 to 4.0 ng/mL). Prostate adenocarcinoma was diagnosed on February 24, 2004, 42 days after the ustekinumab dose.

*Comment: The presence of disease pretreatment is evidenced by the elevated PSA one week post dose. This event was not related to study agent.*

Subject T08-021-041: prostate adenocarcinoma

The subject was a 59 y/o male who received ustekinumab 45 mg on March 28 (Week 0), April 25, July 18 and October 17, 2006. Prostate adenocarcinoma was diagnosed on November 2, 2006. He had had progressive increase in his PSA levels (normal ranges not provided): July 2004: 2.76; December 2004: 3.98; October 2006: 5.71.

He underwent a radical retropubic prostatectomy with pelvic lymph node dissection (hospital admission date: \_\_\_\_\_, which revealed evidence of metastatic disease (2 of 5 pelvic nodes and 1 of 5 periprostate nodes were positive for metastatic disease). Post-operative PSA values were: January 2007: 1.31; March 2007: 0.05.

*Comment: The progressive rise in PSA prior to ustekinumab exposure suggests that onset of the prostate disease pre-dated the ustekinumab exposure. While the reviewer does not consider that ustekinumab was causative, it is possible that ustekinumab might have had some permissive role in the aggressiveness (metastasis) of the cancer. Previous treatment for this subject's psoriasis included efalizumab.*

Subject T08-029-010: transitional cell carcinoma (left kidney)

The subject was a 61 y/o male who received ustekinumab 45 mg on March 9 (Week 0), April 11, June 29, September 21 and December 14, 2006. The subject contacted the study site sometime in January (date not provided) to report that a "tumor" had been found on his left kidney. He was diagnosed with a malignant kidney tumor on \_\_\_\_\_, and underwent nephrectomy the same day (Study Day 350), \_\_\_\_\_ after the last dose.

*Comment: Previous therapy for psoriasis included methotrexate. This subject also suffered a post-operative MI on the day of his nephrectomy.*

Subject T08-109-022: multifocal papillary microcarcinoma of the thyroid

The subject was a 44 y/o male who received ustekinumab 45 mg on March 30 (Week 0), April 27, July 13, October 13, and December 6, 2006. He was diagnosed with a multi-nodular goiter on October 12, 2006. He was diagnosed with hypothyroidism and thyroid carcinoma on \_\_\_\_\_ after 4<sup>th</sup> dose), and thyroidectomy was performed on the same date.

The pathology report of the thyroid tissue is said to have revealed 3 "spots of micropapular thyroid carcinosis", 2 in the right lobe, one in the left. One of the foci in the right lobe exhibited "superficial invasion of the thyroid parenchyma with evidence of vascular invasion, extrathyroid extension or contact at the resection margin." The subject was to have started preventive treatment with radioactive iodine on an unspecified date in February 2007.

**Comment:** Previous psoriasis treatment included methotrexate, infliximab and cyclosporine. It is unclear why the subject received an additional dose of ustekinumab after his diagnosis of malignancy, since treatment was to have been discontinued under these circumstances (i.e. with a diagnosis of malignancy). It is noted too that cyclosporine was an "ongoing" medication as of February 20, 2007.

Subject T08-112-012: infiltrating ductal breast cancer

The subject was a 41 y/o female. She received ustekinumab 45 mg on March 13 (Week 0), April 11, July 4, September 26, November 21, 2006 and January 16, 2007.

She noted a mass in her left breast on February 25, 2007. A mammogram was done March 11, 2007 and revealed a 1.6-cm mass and several enlarged lymph nodes in the left axilla. She underwent ultrasound-guided biopsy and was diagnosed with infiltrating ductal carcinoma of left breast on [REDACTED]. A smaller satellite lesion was found peripheral to the larger mass. She underwent a radical lumpectomy and lymph node biopsy on [REDACTED]. Three (3) of 12 lymph nodes were positive. An abdominal ultrasound scan showed no abnormal mass in the liver and a whole body bone scan showed no osseous metastases. She received 3 cycles of adjuvant chemotherapy, after which she was to have undergone local radiation and treatment with tamoxifen.

b(6)

**Comment:** Previous psoriasis treatment included alefacept and onercept (The latter is not approved for psoriasis. Per medicalnewstoday.com, onercept is a recombinant tumor necrosis factor binding protein, and the psoriasis development program was discontinued because of an unfavorable risk-benefit profile). Her risks factors for breast cancer include long-term use of oral contraceptives (18 years) and late birth of children (first child at 38).

Generally, the possibility that ustekinumab did not impact tumor behavior (e.g. rate of growth, metastasis) cannot be excluded.

Subject T09-007-028: hepatocellular carcinoma

The subject was a 63 y/o M who received placebo treatment on May 30, 2006. On June 10 (Day 12), he was diagnosed with hepatic cirrhosis and portal hypertension. He was also noted to have ascites. Abdominal ultrasound done June 14 revealed a lesion suspicious for hepatocellular carcinoma. CT scan of liver done June 30 (Day 32) suggested hepatocellular carcinoma. No pathologic study was planned; the opinion of 2 hepatologists was hepatocellular carcinoma.

Other Serious Adverse Events through the End of the Reporting Period

The remaining serious adverse are presented in the following table.

Serious Adverse Events Through the End of the Reporting Period Source Appendix B.23 of ISS  
 CNTO 1275

	Placebo	Placebo → 45 mg	Placebo → 90 mg	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
Subjects with 1 or more serious adverse events	11 (1.5%)	10 (3.1%)	6 (1.6%)	32 (4.1%)	27 (3.4%)	75 (3.3%)

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

Psychiatric disorders	1 (0.1%)	2 (0.6%)	0 (0.0%)	2 (0.3%)	3 (0.4%)	7 (0.3%)
Psychotic disorder	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
Alcohol withdrawal syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Delirium	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Depression	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Polysubstance dependence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Schizophrenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Suicide attempt	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Musculoskeletal and connective tissue disorders	1 (0.1%)	1 (0.3%)	0 (0.0%)	5 (0.6%)	0 (0.0%)	6 (0.3%)
Intervertebral disc protrusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	0 (0.0%)	2 (0.1%)
Dactylitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Intervertebral disc degeneration	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Osteoarthritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Pain in extremity	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Psoriatic arthropathy	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

	Placebo	CNTO 1275				Combined
		Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg	
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
Subjects with 1 or more serious adverse events	11 (1.5%)	10 (3.1%)	6 (1.6%)	32 (4.1%)	27 (3.4%)	75 (3.3%)
<b>Injury, poisoning and procedural complications</b>						
Injury, poisoning and procedural complications	0 (0.0%)	1 (0.3%)	0 (0.0%)	4 (0.5%)	0 (0.0%)	5 (0.2%)
Anaesthetic complication	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Clavicle fracture	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Open fracture	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Rib fracture	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Seroma	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
<b>General disorders and administration site conditions</b>						
General disorders and administration site conditions	2 (0.3%)	1 (0.3%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	3 (0.1%)
Chest pain	1 (0.1%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.1%)
Non-cardiac chest pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Chest discomfort	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Renal and urinary disorders</b>						
Renal and urinary disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	1 (0.1%)	3 (0.1%)
Calculus ureteric	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Nephrolithiasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Renal failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
<b>Respiratory, thoracic and mediastinal disorders</b>						
Respiratory, thoracic and mediastinal disorders	2 (0.3%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	3 (0.1%)
Acute respiratory distress syndrome	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Dyspnoea	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Pneumonitis	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Respiratory failure	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Asthma	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Investigations</b>						
Investigations	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
Blood pressure increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Hepatic enzyme increased	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
<b>Metabolism and nutrition disorders</b>						
Metabolism and nutrition disorders	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)	2 (0.1%)
Hypocalcaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Hypokalaemia	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
<b>Pregnancy, puerperium and perinatal conditions</b>						
Pregnancy, puerperium and perinatal conditions	0 (0.0%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
Abortion spontaneous	0 (0.0%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
<b>Vascular disorders</b>						
Vascular disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
Hypertension	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
<b>Ear and labyrinth disorders</b>						
Ear and labyrinth disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Vertigo	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
<b>Endocrine disorders</b>						
Endocrine disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Goitre	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
<b>Hepatobiliary disorders</b>						
Hepatobiliary disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
Cholecystitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.0%)
<b>Skin and subcutaneous tissue disorders</b>						
Skin and subcutaneous tissue disorders	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Psoriasis	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Pityriasis rubra pilaris	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

**Comment:** For the remaining serious adverse events, intervertebral disc protrusion and spontaneous abortion were the only events for which there was more than one report: 2 reports of each event; both of the former in the 45 mg group, and both of the latter in the placebo → 90 mg crossover group.

### 7.3.3 Dropouts and/or Discontinuations

#### Through Week 12

The percentages of subjects who discontinued study agent due to an adverse event were similar between treatment groups. Specifically, 14 of 732 subjects (1.9%) in the placebo group discontinued study agent due to an adverse event, 9 of 790 subjects (1.1%) in the 45 mg group, and 11 of 792 subjects (1.4%) in the 90 mg group. Most of these events were reported in one subject each with the exception being in the Skin and subcutaneous tissue disorders system organ class, and in this category, the majority of events were reported in subjects treated with placebo:

#### **Discontinuations due to adverse events through Week 12: Skin and subcutaneous tissue disorders system (Source: Appendix B.27 ISS)**

	Placebo n=732	Ustekinumab 45 mg n=790	Ustekinumab 90 mg n=792
Skin and subcutaneous tissue disorders	9 (1.2%)	1 (0.1%)	0 (0.0%)
Psoriasis	5 (0.7%)	1 (0.1%)	0 (0.0%)
Dermatitis exfoliative	2 (0.3%)	0 (0.0%)	0 (0.0%)
Pustular psoriasis	1 (0.1%)	0 (0.0%)	0 (0.0%)
Rash generalized	1 (0.1%)	0 (0.0%)	0 (0.0%)

System organ classes for which there were more than 2 reports of adverse events that led to discontinuation of study agent in ustekinumab-treated subjects are presented in the following table.

#### **Discontinuations due to adverse events through Week 12 (Source: Appendix B.27 ISS)**

System organ class Preferred term	Placebo n=732	Ustekinumab 45 mg n=790	Ustekinumab 90 mg n=792
# discontinued	14 (1.9%)	9 (1.1%)	11 (1.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	2 (0.3%)	2 (0.3%)
Basal cell carcinoma	0 (0.0%)	1 (0.1%)	1 (0.1%)
Meningioma benign	0 (0.0%)	0 (0.0%)	1 (0.1%)
Prostate cancer	0 (0.0%)	1 (0.1%)	0 (0.0%)
Infections and infestations	1 (0.1%)	0 (0.0%)	3 (0.4%)
Cellulitis	1 (0.1%)	0 (0.0%)	1 (0.1%)
Herpes zoster	0 (0.0%)	0 (0.0%)	1 (0.1%)
Pneumonia	0 (0.0%)	0 (0.0%)	1 (0.1%)
Psychiatric disorders	1 (0.1%)	2 (0.3%)	1 (0.1%)
Alcohol withdrawal syndrome	0 (0.0%)	0 (0.0%)	1 (0.1%)
Alcoholism	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anger	0 (0.0%)	1 (0.1%)	0 (0.0%)
Anxiety	0 (0.0%)	1 (0.1%)	0 (0.0%)
Psychotic disorder	1 (0.1%)	1 (0.1%)	0 (0.0%)
Cardiac disorders	0 (0.0%)	0 (0.0%)	2 (0.3%)

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

Acute myocardial infarction	0 (0.0%)	0 (0.0%)	1 (0.1%)
Palpitations	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ventricular extrasystoles	0 (0.0%)	0 (0.0%)	1 (0.1%)
Nervous system disorders	0 (0.0%)	2 (0.3%)	0 (0.0%)
Cerebrovascular accident	0 (0.0%)	1 (0.1%)	0 (0.0%)
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)

**Comment:** Two subjects in the placebo group discontinued study agent because of a malignancy or a malignancy-related adverse event, but are not listed in this system-organ class:

- Subject T09-007-028 discontinued study agent for ascites, which resulted from the serious adverse event of hepatocellular carcinoma (unclear why the reason for discontinuation was not the former, since protocols specified discontinuation of study agent for development of a malignancy).
- Subject T09-125-001 discontinued study agent because of skin cancers (2 squamous cell carcinomas).

There was no apparent pattern of adverse events leading to discontinuation of study agent.

#### Through the End of the Reporting Period

Through the end of the reporting period, 2% of subjects in the placebo group, 1.9% in the placebo → 45 mg, 0.8% in the placebo → 90 mg groups, and 3% of subjects in the 45 mg and 90 mg dosing groups discontinued due to an adverse event. The proportions of subjects who discontinued due to an adverse event were generally similar between treatment groups.

“Neoplasms benign, malignant, and unspecified” was again the most frequently reported system-organ class leading to study agent discontinuation. Rates of adverse events leading to study agent discontinuation in this category were all ≤1%. System organ classes for which there were more than two reports of adverse events leading to discontinuation of study agent in ustekinumab-treated subjects are presented in the following table:

**Discontinuations due to adverse events through the End of the Reporting Period Source: Appendix B.28 ISS**

System organ class Preferred term	Placebo n= 7832	Placebo → 45 mg n=320	Placebo → 90 mg n=364	45 mg n=790	90 mg n=792
# discontinued	15 (2.0%)	6 (1.9%)	3 (0.8%)	24 (3.0%)	24 (3.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	2 (0.6%)	0 (0.0%)	8 (1.0%)	6 (0.8%)
Basal cell carcinoma	0 (0.0%)	2 (0.6%)	0 (0.0%)	3 (0.4%)	4 (0.5%)
Prostate cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	0 (0.0%)
Breast cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Meningioma benign	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Neoplasm malignant	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Squamous cell carcinoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Squamous cell carcinoma of skin	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Thyroid gland cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Infections and infestations	1 (0.1%)	1 (0.3%)	0 (0.0%)	3 (0.4%)	6 (0.8%)
Cellulitis	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.3%)
Hepatitis c	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Herpes zoster	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Meningitis aseptic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

Osteomyelitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Pneumonia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Urinary tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Viral infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Wound infection	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	5 (0.6%)
Acute myocardial infarction	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Coronary artery disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Angina pectoris	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Myocardial infarction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Palpitations	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Ventricular extrasystoles	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Nervous system disorders	0 (0.0%)	1 (0.3%)	1 (0.3%)	4 (0.5%)	1 (0.1%)
Headache	0 (0.0%)	1 (0.3%)	0 (0.0%)	2 (0.3%)	0 (0.0%)
Cerebrovascular accident	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	0 (0.0%)
Chorea	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Dizziness	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Pregnancy, puerperium and perinatal conditions	1 (0.1%)	0 (0.0%)	1 (0.1%)	2 (0.3%)	2 (0.3%)
Pregnancy	1 (0.1%)	0 (0.0%)	1 (0.1%)	2 (0.3%)	1 (0.1%)
Psychiatric disorders	1 (0.3%)	1 (0.3%)	0 (0.0%)	3 (0.4%)	0 (0.0%)
Anxiety	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	0 (0.0%)
Alcohol withdrawal syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Alcoholism	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anger	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Delirium	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Psychotic disorder	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Skin and subcutaneous tissue disorders	10 (1.4%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	1 (0.1%)
Psoriasis	6 (0.8%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	1 (0.1%)
Dermatitis exfoliative	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pustular psoriasis	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rash generalized	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

*Comment: There was no apparent dose response in the pattern of adverse events leading to study agent discontinuation.*

### 7.3.4 Significant Adverse Events

This section will discuss adverse drug reactions and further discuss occlusive vascular events, malignancies, and diverticulitis.

#### Adverse Drug Reactions

Citing ICHE6, the applicant defined adverse drug reactions as those adverse events for which “there was some basis to believe there was a causal relationship between (ustekinumab) and the (adverse event).” Factors the applicant considered in making a determination of whether an adverse event should be assessed as an adverse drug reaction included:

1. the seriousness of the event

2. the frequency of reporting
3. whether the adverse event rate for the drug exceeded the placebo rate
4. the extent of dose-response
5. the extent to which the adverse event was consistent with the pharmacology of the drug
6. the timing of the event relative to the time of drug exposure
7. existence of challenge and dechallenge experience

Using data from earlier studies (prior to unblinding of Phase 3 results) and blinded data from ongoing clinical studies, the applicant had “previously” determined that the following events were adverse drug reactions:

- Diarrhea
- Fatigue
- Injection-site reactions
- Cellulitis
- Nasopharyngitis
- Upper respiratory tract infection

At the conclusion of the Phase 3 studies, unblinded data from the Phase 3 studies combined with data from other clinical studies was evaluated. Adverse events were evaluated as potential adverse drug reactions primarily based on the frequency of reporting, whether the adverse event rate for the drug exceeded the placebo rate, and the extent of dose-response. Analyses generally utilized pooled safety data from the Phase 2 and Phase 3 psoriasis clinical studies and generally used the previously described cut-offs (i.e. Through Week 12 placebo-controlled period and through end of the reporting period).

The applicant established thresholds to identify potential adverse drug reactions based on event frequency, relative risk versus placebo, and extent of dose-response. Adverse events were considered to be potential adverse drug reactions if they occurred in at least 1% of ustekinumab-treated subjects and had a relative risk of  $\geq 1.5$ -fold in ustekinumab-treated subjects compared with placebo-treated subjects or in magnitude of dose response.

From the database analyzed for the ISS, adverse events that occurred at least 1.5-fold more frequently in ustekinumab-treated versus placebo-treated subjects or that showed a dose-response trend and therefore represent possible adverse drug reactions were: pharyngolaryngeal pain, nasal congestion, viral upper respiratory tract infection, diarrhea, injection-site erythema, ecchymosis, pruritus, headache, depression, back pain, myalgia, dizziness, and skin laceration (see table of Adverse events in  $\geq 1\%$  of ustekinumab treated subjects through the end of the reporting period in Section 7.4.1).

***Comment:*** *In the reviewer’s opinion, the applicant has applied reasonable criteria to make a determination of when an adverse event might represent an adverse drug reaction. However, this list may need to be modified (e.g. expanded) as additional information becomes available about their product from ongoing clinical trials and from the marketplace.*

**Occlusive Vascular Events**

The applicant conducted analyses to assess for potential impact of ustekinumab on serious cardiovascular/cerebrovascular events

Number of serious ischemic cardiovascular events, serious cerebrovascular events and sudden cardiac death through the end of the reporting period; treated subjects in psoriasis Phase 2 and Phase 3 (Appendix B. 58 of ISS):

	Placebo	45 mg	90 mg	Combined
Subjects treated*	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
<b>Type of events</b>				
<b>Serious myocardial infarction events</b>				
Observed number of events	1	2	3	5
Event rate per 100 subject-years	0.55	0.28	0.40	0.34
95% confidence interval <sup>b</sup>	(0.01, 3.06)	(0.03, 1.00)	(0.08, 1.18)	(0.11, 0.80)
<b>Serious stroke events</b>				
Observed number of events	0	3	0	3
Event rate per 100 subject-years	0.00	0.41	0.00	0.20
95% confidence interval <sup>b</sup>	(0.00, 1.64)	(0.09, 1.21)	(0.00, 0.40)	(0.04, 0.60)
<b>Sudden cardiac death</b>				
Observed number of events	0	0	1	1
Event rate per 100 subject-years	0.00	0.00	0.13	0.07
95% confidence interval <sup>b</sup>	(0.00, 1.64)	(0.00, 0.41)	(0.00, 0.75)	(0.00, 0.38)
<b>Sudden cardiac death, serious myocardial infarction events, or serious stroke events</b>				
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>b</sup>	(0.01, 3.06)	(0.22, 1.61)	(0.15, 1.38)	(0.28, 1.16)
<b>Serious ischemic cardiovascular events and cerebrovascular events</b>				
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>b</sup>	(0.01, 3.06)	(0.39, 1.99)	(0.38, 1.94)	(0.52, 1.60)

\* Placebo crossover subjects are included in CNTO 1275 columns after crossover to CNTO 1275.

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

*Comment: Patients with psoriasis are said to be at increased risk for occlusive vascular disease and cardiovascular disease.<sup>9,10,11,12</sup> Psoriasis may itself be an independent risk factor for MI.<sup>9,12</sup> Subjects with more severe disease (as with the applicant's target population) may have a higher risk than those with mild disease, and this may be reflective of the role of chronic inflammation in contributing to atherosclerotic and MI risk.<sup>9,12</sup> Co-morbidities that increase the risk of occlusive vascular events are common in the psoriasis population (and the baseline medical history of the study population appear to reflect this, Section 7.2.1).<sup>11,12</sup>*

*Rates of any serious ischemic cardiovascular event, serious cerebrovascular event or sudden cardiac death were similar between treatment groups through the end of the reporting period, suggesting no impact of ustekinumab on these risks.*

### Malignancies

A total of 21 subjects had malignancies through the end of the reporting period, 19 of whom received ustekinumab. Of those 19 subjects, 14 had nonmelanoma skin cancers (NMSC), 6 in the 45 mg group; 8 in the 90 mg group. The remaining 5 had malignancies that were reported as serious adverse events and have been previously discussed (see Section 7.3.2).

The 2 malignancies that were reported through the end of the reporting period in the placebo group were hepatocellular carcinoma (reported as a serious adverse event) and SCC (skin).

*Comment: A 3rd subject in the placebo group reported 3 SCC (one invasive); however, these events were miscoded as screening adverse events. This subject is not reflected in the data presented in the table below.*

Of the 14 ustekinumab-treated subjects who had NMSC, 4 had multiple lesions:

- Subject T04-003-005: 70 y/o M with history of BCC was diagnosed with 2 basal cell carcinomas (BCC), one of which was reported during the placebo period; one was reported after crossover to receive a single 90 mg dose of ustekinumab.
- Subject T04-014-007 (45 mg single dose): 79 y/o M with history of BCC was diagnosed with 3 BCC (2 were diagnosed 34 days after the dose of ustekinumab).
- Subject T08-020-009 (90 mg group) had 5 BCC and reported 5 more BCC after the end of the reporting period (This subject is discussed further below.)
- Subject T09-002-012 (45 mg group): 61 y/o F with history of BCC was diagnosed with 1 BCC and 1 squamous cell carcinoma (SCC) on the day after her 3<sup>rd</sup> dose of study agent (Day 128).

In summary, a total of 21 NMSC were reported in 14 subjects treated with ustekinumab.

*Comment: Development of new lesions is not uncommon in individuals with a history of NMSC, and most of these subjects had such prior history (3 of 4). For these subjects, the provided information does not suggest a role for ustekinumab in the development of the new lesions in the reviewer's opinion. The 4<sup>th</sup> subject is described below.*

#### Subject T08-020-009

This 58 y/o male had 5 BCC diagnosed (all on torso, i.e. back, chest, abdomen). Three were diagnosed on Day 300, 13 days after his 5<sup>th</sup> (and last) dose of 90 mg. Two additional lesions were identified 2 weeks later on Day 314. Approximately 4 months later (after the end of the reporting period), 5 additional BCC were reported, and all were again on the torso. He had no personal or family history suggestive of basal cell nevus syndrome, no history of NMSC, x-ray treatments, bad sunburns or extensive sun exposure or UVB treatments. No history was provided regarding possible arsenic exposures (although SCC more often the type of NMSC in this setting). Tanning bed use was not specifically addressed. His previous psoriasis therapies were topical and PUVA (the latter for approximately 6 months). He was not reported to have been on any immunosuppressive treatments.

*Comment: This presentation is unusual. The distribution and numbers of lesions are rather striking. No history was provided on which to base a theory for concentration of BCC on the*

*trunk. While the trunk can represent a sun-exposed area (e.g. shirtless outdoor activities), it is unusual that no lesions were reported on other sun-exposed areas, e.g. face, forearms, and in the reviewer's opinion, and these are areas that generally would likely have received more cumulative exposure. Additionally, this subject reportedly had no previous history of NMSC. Given the slow growth of BCC, the reviewer does not consider it likely that ustekinumab was causative; however, some role for ustekinumab in the unusual presentation for this subject cannot be excluded.*

*There is data from animal models suggesting that UV-induced tumors may behave more aggressively in animals deficient in IL-12/23 (see Section 4.3). This may have implications for some patients with psoriasis whose previous treatments might have placed them at increased risk for skin cancer, e.g. PUVA (increased risk of SCC and melanoma with sufficient cumulative exposures). However, it is not clear to what extent, if any, that the animal data might apply to humans.*

The remainder of this page is left intentionally blank.

Number of subjects with 1 or more malignancies through the end of the reporting period; treated subjects in psoriasis Phase 2 and Phase 3 (Table 14 from ISS)

	Placebo	45 mg	90 mg	Combined
Subjects treated <sup>a</sup>	732	1110	1156	2266
<b>Type of malignancy</b>				
<b>Nonmelanoma skin cancer</b>				
Total subject-years of follow-up	182	723	740	1463
Median subject-years of follow-up	0.2	0.5	0.5	0.5
Observed number of subjects	1	6	8	14
Incidence per 100 subject-years	0.55	0.83	1.08	0.96
95% confidence interval <sup>b</sup>	(0.01, 3.06)	(0.30, 1.81)	(0.47, 2.13)	(0.52, 1.61)
<b>Malignancies other than nonmelanoma skin cancer</b>				
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	1	5	0	5
Incidence per 100 subject-years	0.55	0.69	0.00	0.34
95% confidence interval <sup>b</sup>	(0.01, 3.06)	(0.22, 1.61)	(0.00, 0.40)	(0.11, 0.80)
<b>All malignancies</b>				
Total subject-years of follow-up	181	722	740	1461
Median subject-years of follow-up	0.2	0.5	0.5	0.5
Observed number of subjects	2	11	8	19
Incidence per 100 subject-years	1.10	1.52	1.08	1.30
95% confidence interval <sup>b</sup>	(0.13, 3.98)	(0.76, 2.73)	(0.47, 2.13)	(0.78, 2.03)

<sup>a</sup> Placebo crossover subjects were included in CNTO 1275 columns after crossover to CNTO 1275.

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

**Comment:** The above table does not include the placebo-treated subject who reported 3 SCC (miscoded as screening events), which would have increased (doubled) the rate for NMSC in the placebo group, and the rates would then become similar between the placebo and 90 mg groups and become lowest for the 45 mg group. There were no "other" malignancies in the 90 mg group, and the rates were generally similar between placebo and 45 mg (the latter being slightly higher). For all malignancies the rates were generally similar across all 3 treatment groups (and would have been highest for the placebo group, had the subject described above been factored in).

### Diverticulitis

There were nine reports of diverticulitis in subjects who received ustekinumab, and none in subjects who received only placebo. Three of these reports were considered serious and are presented in narrative below. The remaining 6 reports are presented in tabular form below. The applicant did not propose any theory about the occurrence of these events the significance of these findings is unclear.

#### Subject T09-115-033: diverticular perforation, wound infection staphylococcal, respiratory failure, sepsis

This subject was a 41 y/o female who received one dose of ustekinumab 45 mg, and the date of that dose was October 12, 2006 (Week 12). On \_\_\_\_\_, after only dose), she experienced a diverticular perforation, and was admitted to the hospital on the same day. On \_\_\_\_\_, she underwent a Hartman's procedure. However, she suffered complications of necrosis and retraction of the ostomy into the abdominal cavity with development of an intra-abdominal abscess. She developed a MRSA wound infection on \_\_\_\_\_ and this event was said to be resolved on \_\_\_\_\_. She underwent repositioning of the colostomy and drainage of the abscess on \_\_\_\_\_ with partial bowel resection. However, the abdominal wall could not be closed due to bowel swelling and necrotizing fasciitis involving the anterior abdominal wall fascia, and the wound was closed with mesh. The post-operative course was complicated by sepsis and respiratory failure requiring ventilatory support. Onset date for the sepsis and respiratory failure was \_\_\_\_\_ and date of resolution for both was \_\_\_\_\_. She was discharged on \_\_\_\_\_. At discharge, she was tolerating a regular diet and her ostomy was functioning satisfactorily. Additionally, the abdominal wound was assessed as being ready for vacuum assisted closure.

b(6)

*Comment: The reviewer considers that a complicated hospital course could befall anyone with an intestinal perforation (i.e. in the absence of ustekinumab exposure). While one can not exclude the possibility that the single dose of ustekinumab contributed to the course of the infectious complications, the reviewer does not consider it likely.*

#### Subject T-09-129-012: peritonitis; diverticulitis

This subject was a 49 y/o male who received ustekinumab on August 9, September 5 and November 28, 2006. Previous psoriasis treatment included etanercept. On \_\_\_\_\_, after 3<sup>rd</sup> and last dose) he was taken to the emergency room by ambulance with severe lower abdominal pain, chills and vomiting (several episodes). That same day he was diagnosed with peritonitis and diverticulitis. He was treated with IV cefoxitin and pain medication. CT scan of the abdomen and pelvis showed "inflammation with possible foci of free air in a loop of the distal ileum adjacent to and possibly demonstrating a fistulous connection to the sigmoid colon, pneumoperitoneum most likely due to diverticulitis versus primary small bowel perforation, with adhesions/fistulous connection to the sigmoid colon." An abdominal series was done on \_\_\_\_\_ and showed "air and stool throughout the colon, with no significant air-fluid collections, and no evidence of free air." Blood cultures taken on \_\_\_\_\_ showed no growth after 5 days. He was discharged on \_\_\_\_\_ on oral ciprofloxacin, metronidazole, and probiotic acidophilus.

b(6)

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

**Comment:** *The reviewer finds nothing unusual about this subject's uncomplicated hospital course.*

**Subject T09-300-003: diverticulitis**

This was a 48 y/o male whose previous psoriasis treatment included alefacept, efalizumab and "other (certolizumab or placebo). He received ustekinumab on July 24, August 21 and November 13, 2006. On \_\_\_\_\_ after his 3<sup>rd</sup> and last dose), he was diagnosed with a severe serious adverse event of diverticulitis. He was admitted to the hospital on that same date with a history of pain in the left iliac fossa region and fever. His leukocyte count was 85,000. He was begun on amoxicillin and metronidazole. He was afebrile. An abdominal pelvic scan revealed sigmoid diverticulitis with a 17 mm peri-colic abscess, and his antibiotics were changed to amoxicillin and ciprofloxacin. Repeat abdominal pelvic scan revealed a decrease in the size of the abscess. He was discharged on \_\_\_\_\_ and was to continue antibiotics for an additional 8 days. On \_\_\_\_\_ he underwent a laparoscopic left hemicolectomy.

b(6)

**Comment:** *The reviewer finds nothing unusual about this subject's uncomplicated hospital course.*

Diverticulitis		Sources: Attachment 5 of study reports for T08 and T09		
Subject	Age/Sex	Dose	Serious Event (Verbatim)	Other History
T08-016-037	50 M	90 mg	exacerbation of diverticulitis 53 d post 4 <sup>th</sup> dose (Day 253)	tx'd w/ flagyl levaquin; initial dx of diverticulitis 2004 w/"occasional" episodes" since then; 1 subsequent dose of ustekinumab
017-007	38 M	pcb to 45 mg	diverticulitis 54 d post 2 <sup>nd</sup> dose (Day 168)	4 subsequent doses; no inflammation on colonoscopy; dx later changed to tenesmus
018-015	57 M	90 mg	diverticulitis 11 d post 2 <sup>nd</sup> dose (Day 40)	clinical dx; tx'd doxycycline and oxycodone; 2 subsequent doses (colonoscopy said not to reveal diverticulitis)
T09 007-002	58 F	pcb to 45 mg	diverticulitis 17d post 2 <sup>nd</sup> dose (Day 131)	confirmed by CT scan (w/microperforation); antibiotic tx w/cipro & flagyl,
007-039	53M	90 mg	diverticulitis 45 d post 2 <sup>nd</sup> dose (Day 75)	clinical dx; tx'd w/cipro flagyl; 1 subsequent dose
300-006	57M	90 mg	76 d post 2 <sup>nd</sup> dose (Day 105)	hx of diverticulosis since 1987; received 1 subsequent dose

**Comment:** *Some subjects had a history of diverticular disease (e.g. Subject 300-006) including recurrent episodes of diverticulitis that predated exposure to ustekinumab (e.g. Subject T08-016-03). Most continued treatment, receiving at least one additional dose with no reports of recurrence of abdominal complaints. It is noted too that the diagnosis is questionable for certain subjects (e.g. Subjects 017-0070 and 18-015 had no inflammation on colonoscopy). The role of ustekinumab, if any, is unclear. The reviewer found no information suggesting that this is a comorbidity associated with the psoriasis population (e.g. in the way that diabetes or occlusive vascular disease are reported to be). This will be among the events to monitor post marketing. Interestingly, there were no reports of diverticulitis in the data submitted from development of the product for other indications (see Section 7.4.1).*

### Injection Site Reactions

Ustekinumab is packaged in vials of 0.5cc (45mg) and 1.0 cc (90 mg). Therefore, to protect the blind, subjects in the clinical studies received two injections of 0.5 cc and 1.0 cc of study agent, e.g. subjects in the 45 mg treatment group received 0.5 cc of ustekinumab and 1.0 cc of placebo. Thus, the potential existed for subjects to have injection site reactions to both the active and placebo agents, and the analyses reflected this potential, e.g. if a subject exhibited a reaction to both active and placebo, each of these reactions was captured in the appropriate treatment group. "Injection site erythema" was the only reaction reported in > 1% of ustekinumab-treated subjects. The following table presents the reactions for which there were at least two reports in ustekinumab-treated subjects:

**Injection site reactions with > 1 in ustekinumab-treated subjects through the end of the reporting period (Appendix B.36 of ISS)**

	Placebo Injection	45 mg Injection	90 mg Injection
Treated subjects by study agent injection received	2304	1112	1158
Avg number of injections	7.8	3.4	3.2
Total number of injections	17939	3768	3712
Injections with injection-site reactions	76 (0.4%)	36 (1.0%)	49 (1.3%)
Subjects with 1 or more injection-site reactions	60 (2.6%)	30 (2.7%)	41 (3.5%)
<b>System-organ class/preferred term</b>			
General disorders and administration site conditions	51 (2.2%)	27 (2.4%)	36 (3.1%)
Injection site erythema	21 (0.9%)	13 (1.2%)	24 (2.1%)
Injection site pain	14 (0.6%)	2 (0.2%)	8 (0.7%)
Injection site swelling	4 (0.2%)	1 (0.1%)	6 (0.5%)
Injection site pruritus	3 (0.1%)	2 (0.2%)	3 (0.3%)
Injection site irritation	2 (0.1%)	3 (0.3%)	1 (0.1%)
Ecchymosis	7 (0.3%)	2 (0.2%)	3 (0.3%)

**Comment:** The rates of injection sites reactions were similar between the placebo and 45 mg group and highest in the 90 mg group. Injection site erythema was the only reaction that might suggest a dose response.

### 7.3.5 Submission Specific Primary Safety Concerns

Primary submission-specific safety concerns relate to the potential for the product to cause immunosuppression and would thus be serious infections, opportunistic infections and malignancies. For the applicant's product, there may be specific concerns in each of these categories:

- Based on the clinical experience in individuals genetically deficient in IL-12/IL-23, specific infections that might arise in patients treated with ustekinumab include those caused by environmental mycobacteria and nontyphoid salmonella. No cases were documented in either category in the safety database.
- The theoretical concern of malignancy based on rodent studies has been previously discussed.

*Comment: In the reviewer's opinion, the database to date does not suggest a malignancy signal; however, the duration of follow-up in the database is too short to definitely speak to this issue, given the long latency period for malignancies. The numbers of subjects are too few to definitively speak to the risk for low frequency events or certain serious infections, opportunistic infections and malignancies.*

*If approved, the applicant's product would enter an arena in which 5 biologics are approved for treatment of psoriasis. Other immunosuppressive therapies are also available for the applicant's target population. It may become increasingly difficult to attach a signal or causality to any one agent in a target population in whom previous immunosuppressive therapies might have played some contributory role. In some patients, the causative/contributory role of ustekinumab in certain events, e.g. malignancy, may be difficult to discern, given that many in the applicant's target population will likely have had previous exposure to at least one immunosuppressive product which could have played some role in events which only manifested during treatment with ustekinumab. For example, 43% of subjects in the Phase 3 studies had had previous treatment for their psoriasis with an approved biologic (see table of "Summary of psoriasis medication history; subjects randomized at Week 0 in psoriasis Phase 2 and Phase 3" in Section 7.2.1). In the reviewer's opinion, the challenges to attribution of causality, of certain events, to a single immunosuppressive agent in a patient who has had exposure to previous immunosuppressive therapy will likely increase as more of these products become available.*

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

#### Through Week 12

Through Week 12, adverse events were most frequently reported in the "infections and infestations" system organ class, and events were reported at similar rates across treatment groups: 23.0% in the placebo group, 26.6% in the 45 mg group, 25.1% in the 90 mg group. The most common adverse events that occurred through Week 12 in  $\geq 1\%$  in at least one of the ustekinumab treatment groups (i.e. 45 mg or 90 mg) and at a greater rate than placebo were: nasopharyngitis (7.9% in the placebo group, 8.4% in the 45 mg group and 8.0% in the 90 mg group) and upper respiratory tract infection (4.4%, 5.7% and 5.2%, respectively). Adverse events that occurred in the first 12 weeks that were in  $\geq 1\%$  in at least one of the ustekinumab treatment groups (i.e. 45 mg or 90 mg) are presented in the following table:

Number of subjects with 1 or more treatment-emergent adverse events (with frequency of  $\geq 1\%$  in CNTO 1275-treated subjects) through Week 12 by MedDRA system-organ class and preferred term; treated subjects in psoriasis Phase 2 and Phase 3  
 (Table 7 in ISS)

	CNTO 1275			
	Placebo	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 adverse events	369 (50.4%)	455 (57.6%)	409 (51.6%)	864 (54.6%)
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%)
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%)

**Through End of the Reporting Period**

Similarly, through the end of the reporting period, adverse events were also most frequently reported in the “infections and infestations” system organ class, and specific events were reported at similar rates across treatment groups: 24.0% in the placebo group, 45.9% in the placebo → 45 mg group, 38.2% in the placebo → 90 mg, 52.3 % in the 45 mg group, and 53.7% in the 90 mg group. The rates of adverse events in this system organ class were somewhat higher in the placebo → 45 mg group when compared to the placebo → 90 group: 45.9% and 38.2%, respectively. The rates were similar between the 45 mg and 90 mg groups: 52.3% and 53.7%, respectively. Nasopharyngitis was the most frequently reported adverse event in this system organ class, being reported for 8.2% of subjects in the placebo group, 17.8% subjects in the placebo to 45 mg group, 11.8% subjects in the placebo to 90 mg group, 15.8% subjects in the 45 mg group, and 19.1% subjects in the 90 mg group. Upper respiratory tract infection was the 2<sup>nd</sup> most frequently reported adverse event in this system organ class, being reported for 5.1% of subjects in the placebo group, 10.3% subjects in the placebo to 45 mg group, 10.2% subjects in the placebo to 90 mg group, 15.3% subjects in the 45 mg group, and 13.0% subjects in the 90 mg group. All other adverse events in this system organ class were reported in < 5% of ustekinumab-treated subjects.

Adverse events that occurred through the end of the reporting period in ≥1% in at least one of the ustekinumab treatment groups subjects and at a greater rate than placebo are presented in the following table:

**Adverse events in ≥1% of ustekinumab treated subjects through the end of the reporting period  
 (Source: Appendix B.11 of ISS)**

	Placebo	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg
Subjects treated	732	320	364	790	792
Avg duration of follow-up (weeks)	12.9	26.4	25.2	37.0	37.2
Avg exposure (weeks)	4.9	17.1	15.0	26.5	26.6
#with ≥1 adverse event	372 (50.8%)	210 (65.6%)	227 (62.4%)	626 (79.2%)	613 (77.4%)
System organ class Preferred term					
Infections and infestations	176 (24.0%)	147 (45.9%)	139 (38.2%)	413 (52.3%)	425 (53.7%)
Nasopharyngitis	60 (8.2%)	57 (17.8%)	43 (11.8%)	125 (15.8%)	151 (19.1%)
Upper respiratory tract infection	37 (5.1%)	33 (10.3%)	37 (10.2%)	121 (15.3%)	103 (13.0%)
Sinusitis	11 (1.5%)	10 (3.1%)	5 (1.4%)	32 (4.1%)	39 (4.9%)
Influenza	5 (0.7%)	14 (4.4%)	10 (2.7%)	30 (3.8%)	31 (3.9%)
Gastroenteritis	9 (1.2%)	7 (2.2%)	10 (2.7%)	30 (3.8%)	27 (3.4%)
Bronchitis	6 (0.8%)	8 (2.5%)	6 (1.6%)	20 (2.5%)	19 (2.4%)
Viral upper respiratory tract infection	3 (0.4%)	7 (2.2%)	8 (2.2%)	20 (2.5%)	12 (1.5%)
Urinary tract infection	5 (0.7%)	1 (0.3%)	3 (0.8%)	19 (2.4%)	21 (2.7%)
Herpes simplex	4 (0.5%)	2 (0.6%)	2 (0.5%)	18 (2.3%)	18 (2.3%)
Pharyngitis	9 (1.2%)	7 (2.2%)	6 (1.6%)	12 (1.5%)	15 (1.9%)
Gastroenteritis viral	4 (0.5%)	3 (0.9%)	3 (0.8%)	16 (2.0%)	11 (1.4%)
Tooth abscess	0 (0.0%)	2 (0.6%)	3 (0.8%)	12 (1.5%)	14 (1.8%)
Ear infection	1 (0.1%)	5 (1.6%)	5 (1.4%)	9 (1.1%)	7 (0.9%)

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

Rhinitis	3 (0.4%)	1 (0.3%)	4 (1.1%)	10 (1.3%)	8 (1.0%)
Tooth infection	0 (0.0%)	0 (0.0%)	2 (0.5%)	14 (1.8%)	6 (0.8%)
Cellulitis	4 (0.5%)	2 (0.6%)	1 (0.3%)	10 (1.3%)	6 (0.8%)
Pneumonia	2 (0.3%)	3 (0.9%)	0 (0.0%)	3 (0.4%)	8 (1.0%)
Otitis media	3 (0.4%)	1 (0.3%)	4 (1.1%)	5 (0.6%)	2 (0.3%)
<b>Musculoskeletal and connective tissue disorders</b>	<b>76 (10.4%)</b>	<b>35 (10.9%)</b>	<b>46 (12.6%)</b>	<b>156 (19.7%)</b>	<b>154 (19.4%)</b>
Arthralgia	22 (3.0%)	8 (2.5%)	11 (3.0%)	49 (6.2%)	47 (5.9%)
Back pain	8 (1.1%)	8 (2.5%)	7 (1.9%)	33 (4.2%)	34 (4.3%)
Myalgia	6 (0.8%)	3 (0.9%)	5 (1.4%)	19 (2.4%)	21 (2.7%)
Shoulder pain	3 (0.4%)	4 (1.3%)	4 (1.1%)	13 (1.6%)	11 (1.4%)
Pain in extremity	5 (0.7%)	1 (0.3%)	3 (0.8%)	12 (1.5%)	12 (1.5%)
Psoriatic arthropathy	12 (1.6%)	1 (0.3%)	0 (0.0%)	13 (1.6%)	8 (1.0%)
<b>Gastrointestinal disorders</b>	<b>50 (6.8%)</b>	<b>32 (10.0%)</b>	<b>28 (7.7%)</b>	<b>111 (14.1%)</b>	<b>129 (16.3%)</b>
Diarrhea	13 (1.8%)	3 (0.9%)	7 (1.9%)	30 (3.8%)	31 (3.9%)
Nausea	11 (1.5%)	9 (2.8%)	4 (1.1%)	25 (3.2%)	24 (3.0%)
Toothache	3 (0.4%)	2 (0.6%)	4 (1.1%)	10 (1.3%)	14 (1.8%)
Vomiting	4 (0.5%)	1 (0.3%)	1 (0.3%)	16 (2.0%)	10 (1.3%)
Abdominal pain	3 (0.4%)	2 (0.6%)	3 (0.8%)	9 (1.1%)	10 (1.3%)
Abdominal pain upper	3 (0.4%)	2 (0.6%)	2 (0.5%)	7 (0.9%)	10 (1.3%)
Dyspepsia	4 (0.5%)	0 (0.0%)	3 (0.8%)	9 (1.1%)	6 (0.8%)
<b>Skin and subcutaneous tissue disorders</b>	<b>58 (7.9%)</b>	<b>34 (10.6%)</b>	<b>26 (7.1%)</b>	<b>123 (15.6%)</b>	<b>115 (14.5%)</b>
Pruritus	10 (1.4%)	2 (0.6%)	3 (0.8%)	24 (3.0%)	24 (3.0%)
Dermatitis contact	1 (0.1%)	5 (1.6%)	4 (1.1%)	12 (1.5%)	11 (1.4%)
Acne	1 (0.1%)	4 (1.3%)	1 (0.3%)	10 (1.3%)	4 (0.5%)
Urticaria	2 (0.3%)	4 (1.3%)	4 (1.1%)	6 (0.8%)	4 (0.5%)
Ecchymosis	3 (0.4%)	1 (0.3%)	0 (0.0%)	5 (0.6%)	11 (1.4%)
Hyperhidrosis	1 (0.1%)	0 (0.0%)	1 (0.3%)	8 (1.0%)	2 (0.3%)
Night sweats	5 (0.5%)	4 (1.3%)	0 (0.0%)	4 (0.5%)	3 (0.4%)
<b>Nervous system disorders</b>	<b>61 (8.3%)</b>	<b>21 (6.6%)</b>	<b>18 (4.9%)</b>	<b>115 (14.6%)</b>	<b>123 (15.5%)</b>
Headache	35 (4.8%)	11 (3.4%)	11 (3.0%)	64 (8.1%)	71 (9.0%)
Dizziness	9 (1.2%)	3 (0.9%)	3 (0.8%)	17 (2.2%)	23 (2.9%)
<b>General disorders and administration site conditions</b>	<b>40 (5.5%)</b>	<b>22 (6.9%)</b>	<b>19 (5.2%)</b>	<b>107 (13.5%)</b>	<b>114 (14.4%)</b>
Fatigue	15 (2.0%)	7 (2.2%)	5 (1.4%)	31 (3.9%)	26 (3.3%)
Injection site erythema	3 (0.4%)	3 (0.9%)	5 (1.4%)	16 (2.0%)	22 (2.8%)
Edema peripheral	6 (0.8%)	2 (0.6%)	3 (0.8%)	11 (1.4%)	11 (1.4%)
Chest pain	3 (0.4%)	1 (0.3%)	0 (0.0%)	7 (0.9%)	11 (1.4%)
Injection site pain	2 (0.3%)	2 (0.6%)	0 (0.0%)	7 (0.9%)	9 (1.1%)
Pyrexia	0 (0.0%)	2 (0.6%)	2 (0.5%)	9 (1.1%)	5 (0.6%)
<b>Injury, poisoning and procedural complications</b>	<b>31 (4.2%)</b>	<b>29 (9.1%)</b>	<b>27 (7.4%)</b>	<b>108 (13.7%)</b>	<b>91 (11.5%)</b>
Skin laceration	3 (0.4%)	5 (1.6%)	6 (1.6%)	10 (1.3%)	18 (2.3%)
Muscle strain	4 (0.5%)	7 (2.2%)	1 (0.3%)	11 (1.4%)	11 (1.4%)
Back injury	3 (0.4%)	5 (1.6%)	3 (0.8%)	13 (1.6%)	4 (0.5%)
Contusion	3 (0.4%)	4 (1.3%)	1 (0.3%)	13 (1.6%)	5 (0.6%)
Joint sprain	0 (0.0%)	1 (0.3%)	2 (0.5%)	13 (1.6%)	5 (0.6%)
Procedural pain	0 (0.0%)	1 (0.3%)	0 (0.0%)	5 (0.6%)	10 (1.3%)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>34 (4.6%)</b>	<b>20 (6.3%)</b>	<b>26 (7.1%)</b>	<b>91 (11.5%)</b>	<b>87 (11.0%)</b>
Cough	12 (1.6%)	7 (2.2%)	6 (1.6%)	20 (2.5%)	23 (2.9%)
Pharyngolaryngeal pain	7 (1.0%)	5 (1.6%)	5 (1.4%)	14 (1.8%)	22 (2.8%)
Nasal congestion	3 (0.4%)	2 (0.6%)	4 (1.1%)	12 (1.5%)	14 (1.8%)
Sinus congestion	4 (0.5%)	2 (0.6%)	4 (1.1%)	12 (1.5%)	11 (1.4%)
Rhinitis	1 (0.1%)	0 (0.0%)	0 (0.0%)	8 (1.0%)	3 (0.4%)

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

Psychiatric disorders	11 (1.5%)	14 (4.4%)	7 (1.9%)	52 (6.6%)	42 (5.3%)
Insomnia	5 (0.7%)	6 (1.9%)	2 (0.5%)	20 (2.5%)	11 (1.4%)
Depression	3 (0.4%)	5 (1.6%)	3 (0.8%)	14 (1.8%)	11 (1.4%)
Anxiety	1 (0.1%)	4 (1.3%)	4 (1.1%)	17 (2.2%)	6 (0.8%)
Investigations	22 (3.0%)	13 (4.1%)	10 (2.7%)	49 (6.2%)	42 (5.3%)
Alanin aminotransferase increased	1 (0.1%)	2 (0.6%)	1 (0.3%)	8 (1.0%)	14 (1.8%)
Aspartate aminotransferase increased	1 (0.1%)	1 (0.3%)	0 (0.0%)	3 (0.4%)	9 (1.1%)
Vascular disorders	15 (2.0%)	11 (3.4%)	6 (1.6%)	36 (4.6%)	36 (4.5%)
Hypertension	12 (1.6%)	8 (2.5%)	5 (1.4%)	23 (2.9%)	21 (2.7%)
Metabolism and nutrition disorders	14 (1.9%)	16 (5.0%)	5 (1.4%)	25 (3.2%)	28 (3.5%)
Hypercholesterolemia	1 (0.1%)	5 (1.6%)	0 (0.0%)	5 (0.6%)	5 (0.6%)
Eye disorders	9 (1.2%)	1 (0.3%)	3 (0.8%)	24 (3.0%)	24 (3.0%)
Conjunctivitis	3 (0.4%)	1 (0.3%)	2 (0.5%)	9 (1.1%)	5 (0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (0.7%)	5 (1.6%)	5 (1.4%)	20 (2.5%)	16 (2.0%)
Skin papilloma	1 (0.1%)	1 (0.3%)	2 (0.5%)	10 (1.3%)	4 (0.5%)
Ear and labyrinth disorders	3 (0.4%)	3 (0.9%)	1 (0.3%)	17 (2.2%)	13 (1.6%)
Vertigo	2 (0.3%)	2 (0.6%)	1 (0.3%)	10 (1.3%)	5 (0.6%)

### Tuberculosis

Subjects with latent tuberculosis diagnosed at screening were eligible for the study participation if active tuberculosis had been excluded out and appropriate treatment had been undertaken (either prior to or simultaneous with first dose of study treatment). A total of 68 subjects met these criteria, and participated in the Phase 3 studies.

Two subjects developed latent tuberculosis after screening, were begun on treatment and continued in the study:

1. Subject C0743T09-002-009

This 34 y/o male had a negative PPD at screening. He developed a positive PPD skin test 58 days after receiving his second dose of 90 mg of ustekinumab. (He had been skin tested at work because a co-worker tested positive). His chest x-ray was reported to be negative and he was treated with isoniazid and pyridoxine. He received a third dose of ustekinumab approximately 28 days after the positive skin test, i.e. study treatment was not discontinued and he remained in the study.

2. Subject C0743T09-013-062

This 70 y/o female was diagnosed with latent tuberculosis on study Day 1 and remained in the study, receiving three doses of ustekinumab by the end of the reporting period.

**Comment:** There were no reports of complications of tuberculosis through the end of the reporting period.

**PHASE 1 STUDIES:**

The applicant conducted 2 Phase 1 studies in the psoriasis development program: C0379T01 and C0379T02:

**C0379T01:** [“A Phase I, Single Ascending Dose, Safety, Tolerability, Pharmacokinetic/ Pharmacodynamic Study of the Human Monoclonal Antibody to Human IL-12 (CNTO 1275, previously referred to as 12B75) in Patients with Moderate to Severe Psoriasis Vulgaris”]

This study was the first-in-human study. It was a multi-center, open-label, dose-ascending, non-randomized study and evaluated single IV administrations of ustekinumab in subjects with moderate to severe psoriasis vulgaris. Cohorts were sequentially administered single doses of either 0.09, 0.27, 0.9, or 4.5 mg/kg of ustekinumab. A total of 18 subjects were enrolled. Subjects remained in the clinical research unit for at least 72 hours after administration of the study drug and returned for periodic follow-up through 16 weeks postdose.

Adverse events were most frequently reported in the following body systems: white cell and reticuloendothelial system disorders (11 of 18 subjects), body as a whole-general disorders (10 of 18 subjects), central and peripheral nervous system disorders (10 of 18 subjects), and respiratory system disorders (9 of 18 subjects).

Commonly reported adverse events included decreases in T-lymphocyte subsets (10 of 18 subjects (variable and no pattern noted), headache (6 of 18 subjects), cold symptoms (5 of 18 subjects), and biopsy incision site pain (4 of 18 subjects). Most adverse events occurred in only 1 or 2 of the 18 subjects. There were no specific adverse events that occurred more frequently at the higher doses (1.0 mg/kg and 5.0 mg/kg).

**C0379T02:** (“A Phase I, Double-blind, Placebo-controlled Study Evaluating the Safety and Pharmacology of Single Subcutaneous (SC) Administrations of Human Monoclonal Antibody to IL-12 (CNTO 1275) in Subjects with Moderate to Severe Psoriasis Vulgaris”)

This was a multicenter, randomized, double-blind, placebo-controlled study of single SC administrations of ustekinumab. A total of 21 subjects were randomized (4 or 5 subjects per cohort) to active or placebo treatment within 1 of 4 sequential escalating dose cohorts (0.27 mg/kg, 0.675 mg/kg, 1.35 mg/kg, or 2.7 mg/kg) across 3 sites. Subjects remained in the clinic for at least 8 hours after administration of study agent and returned for periodic follow-up visits throughout the 24-week study period.

The body systems with the most frequently reported adverse events were respiratory system disorders (9 of 17 subjects in ustekinumab treatment groups, 1 of 4 subjects on placebo), metabolic and nutritional disorders [6 of 19 subjects in ustekinumab treatment groups and 1 of 4 subjects on placebo (all events in this category were CPK elevations; see below)], and white cell and reticuloendothelial system disorders (5 of 17 subjects in ustekinumab treatment groups).

Adverse events were most frequently reported in the following body systems: elevated CPK levels [6 of 17 subjects across the ustekinumab treatment groups (not dose-related) and 1 of 4 subjects on placebo], decreases in lymphocytes and lymphocyte subsets (4 of 17 in ustekinumab treatment groups), and upper respiratory infection (4 of 17 in ustekinumab treatment groups). Of 6 subjects in the ustekinumab groups with elevations in CPK, 3 had elevations prior to receiving any product. Of the 3 whose elevations occurred post-injection, CPK-MB values were within normal limits, and there were no symptoms suggestive of possible etiologies.



The proportions of subjects experiencing “markedly abnormal” hematology and chemistry values were reported to be generally “low and similar” between treatment groups. Elevated non-fasting glucose levels were observed on at least 1 occasion in 11.8% in both treatment groups. Two placebo-treated subjects (5.4%) and 1 ustekinumab-treated subject (2.1%) had a change in fasting glucose from < 126 mg/dL to ≥126 mg/dL at 1 and/or 2 postbaseline visits through Week 12.

A higher proportion of subjects discontinued study agent due to adverse events in the placebo group (5.7%) as compared to the ustekinumab group (1.3%). The most common reason(s) for discontinuation was because of worsening of underlying psoriasis and/or psoriatic arthritis.

*Comment: It is unclear whether “markedly abnormal” was defined as it was in the Phase 3 studies.*

### Crohn’s Disease

One study was conducted for Crohn’s disease, C0379T07 (and the development program is ongoing). The study was a Phase 2a, multicenter, randomized, blinded, placebo-controlled study in 131 subjects with moderately to severely active Crohn’s disease and evaluated

- 4 doses of 90 mg SC ustekinumab or
- 1 dose of 4.5 mg/kg IV ustekinumab placebo

Subjects were followed for safety through Week 28. Two populations were enrolled:

- Population 1: Subjects with moderate to severely active Crohn’s disease, despite treatment with 5-ASA compounds, antibiotics, corticosteroids, and/or immunomodulators, including anti-TNF agents, were treated in the placebo-controlled portion of the study. Subjects were treated with IV or SC ustekinumab with matching placebo. Subjects in either the IV or SC placebo groups crossed over at Week 8 to receive ustekinumab while the subjects randomized to ustekinumab received placebo to maintain the blind.
- Population 2: Subjects who failed to respond to infliximab at the maximum approved dose and treatment regimen for Crohn’s disease as defined in the U.S. package insert were treated in the open label portion of the study. Subjects received IV or SC ustekinumab initially and did not receive additional study agent after Week 8. There was no placebo control in the population.

No deaths occurred during the Crohn’s disease study.

Through Week 8 in Population 1, serious adverse events occurred in 3 (5.8%) subjects in the combined SC and IV placebo group and 2 (3.8%) subjects in the combined SC and IV ustekinumab group. Through Week 28, 6 (6.5%) subjects in Population 1 and 4 (14.8%) subjects in Population 2 had serious adverse events. Most serious adverse events were related to Crohn’s disease. The narratives of the serious adverse events were not presented by Population 1 or 2 in the study report, nor will subjects be presented by treatment group in the following table:

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

**Serious adverse events (Source: Attachment 5 of study report for T07)**

Age/sex (route dosed or treatment group)	Event	Day of event relative to last ustekinumab
31 y/o male (SC)	paranasal sinusitis and syncope	sinusitis 135 days after 4 <sup>th</sup> dose); syncope (2 <sup>nd</sup> episode; 153 days after 4 <sup>th</sup> dose)
24 y/o female (SC)	pancreatitis	(190 days after 4 <sup>th</sup> dose)
62 y/o male (IV)	small bowel obstruction	(35 days after only dose)
30 y/o male (SC)	Crohn's disease with stricture	41 days after 4 <sup>th</sup> dose
63 y/o male (placebo)	exacerbation of Crohn's disease; partial small bowel obstruction	n/a
26 y/o male (placebo)	small bowel stricture and NSAID induced ulcer	n/a
56 y/o female (SC)	infectious gastroenteritis	90 days after 4 <sup>th</sup> dose
53 y/o female (IV)	partial small bowel obstruction	144 days after last dose
57 y/o male (SC)	dehydration	217 days after 4 <sup>th</sup> dose
31 y/o male (IV):	Crohn's terminal ileitis	148 days after only dose
33 y/o female (IV):	1. disseminated histoplasmosis 2. Crohn's flare 3. syncope	1. date not specified 2. 140 days after only dose 3. 188 days post dose dose
56 y/o female (IV):	acute Crohn's flare-up with partial bowel obstruction	319 days after only dose
63 y/o male (SC):	kidney stone and kidney stone-stent placement	107 days after 4 <sup>th</sup> dose and 253 days after 4 <sup>th</sup> dose
42 y/o female (IV):	colon stenosis; pneumothorax	168 days after only dose 172 days after only dose
35 y/o female (placebo):	worsening Crohn's disease; erythema nodosum	n/a
53 y/o male (IV):	1. coronary artery disease 2. prostate cancer	1. diagnosed 2 days after only dose with onset of chest pain 6-7 after infusion 2. 63 days after only dose
47 y/o male (IV):	worsening of pain right infection of right knee incision site lower leg)	320 days after only dose; post knee replacement 323 days after only dose
39 y/o female (SC):	perforated colon; abdominal abscess	1. 304 days after 4 <sup>th</sup> dose 2.322 days after 4 <sup>th</sup> dose

Through Week 8, the proportion of subjects with an adverse event was 71.2% in the combined SC and IV ustekinumab group and 78.8% in the combined SC and IV placebo group. The proportion of subjects with adverse events in the SC ustekinumab group (68.0%) was similar to the proportion in the IV group (74.1%). Gastrointestinal disorders was the system-organ class in which the highest proportion of subjects reported adverse events: 32.7% in the combined SC and IV ustekinumab treatment group compared with 48.1% in the combined SC and IV placebo group. Adverse events occurring in  $\geq 5\%$  of ustekinumab-treated subjects were abdominal pain (11.5% and 11.5%), headache (11.5% versus 15.4%), Crohn's disease (7.7% and 13.5%), upper respiratory tract infection (7.7% and 5.8%), pruritus (5.8% and 0.0%), rash (5.8% and 5.8%), pyrexia (5.8% and 5.8%), arthralgia (5.8% and 5.8%), and anxiety (5.8% and 0.0%).

In the infections and infestations system organ class through Week 8 (in Population 1), there were two events for which there were more than one report in ustekinumab subjects, and both were in subjects treated via the SC route: upper respiratory tract infection [3 subjects (12.0%) and similar to placebo at 11.5%] and nasopharyngitis [2 subjects (8.0%); no reports in other treatment groups]. Upper respiratory tract infection and nasopharyngitis remained the two most common events in this system organ class when both Populations 1 and 2 are considered (i.e.

subjects in ustekinumab arms). In Population 2 through Week 28, upper respiratory tract infection was the most commonly reported adverse event in the infections and infestations system organ class [1 (7.1%) in SC subjects and 3 (23.1%) in IV subjects], followed by “Gastroenteritis viral”, reported only in the IV group in 3 subjects (23.1%).

Malignancies were reported for 2 subjects. In addition to the report of prostate cancer (see serious adverse events), a 43 y/o female (SC) was diagnosed with a basal cell carcinoma (lip; 300 days after 4<sup>th</sup> dose) and squamous cell carcinoma (leg; 320 days after 4<sup>th</sup> dose).

*Comment: The subject diagnosed with the NMSC’s had a history of sunbathing in her youth and reported being a then “current” user of tanning beds.*

The following table presents all events reported in the cardiac disorders system organ class through Week 8 in Population 1 (the placebo-controlled population):

**All Adverse Events Reported in the Cardiac Disorders System Organ Class through Week 8 (Population 1)**  
 Source: Attachement 4.4 of study report for C0379T07

	SC		IV	
	Placebo	CNTO 1275 90 mg	Placebo	CNTO 1275 4.5 mg/kg
Cardiac disorders	2 (7.7%)	0 (0.0%)	1 (3.8%)	2 (7.4%)
Coronary artery disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
Palpitations	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
Angina pectoris	0 (0.0%)	0 (0.0%)	1 (3.8%)	0 (0.0%)
Tachycardia	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

In Populations 1 and 2, through Week 28, 4 cardiac events were reported: atrial flutter in 1 subject (1.7%) in the SC group, and 1 report each of tachycardia (1.7%), coronary artery disease (1.7%) and palpitations (1.7%) all in the IV group.

**Multiple Sclerosis**

\_\_\_\_\_ . The applicant conducted two studies in subjects with MS.  
 C0379T03 was a Phase 1 dose-escalating study in 20 subjects and evaluated 4 single doses of ustekinumab (maximum dose of 2.7 mg/kg) versus placebo. Subjects were followed for safety through Week 16.

C0379T06 was a Phase 2 multicenter, double-blind, placebo-controlled, randomized study of 249 subjects and evaluated 4 dose regimens (200 subjects were randomized to ustekinumab treatment):

- 27 mg at Weeks 0, 1, 2, 3, 7, 11, 15, and 19
- 90 mg at Weeks 0, 1, 2, 3, 11, and 19; Placebo at Weeks 7 and 15
- 90 mg at Weeks 0, 1, 2, 3, 7, 11, 15, and 19
- 180 mg at Weeks 0, 1, 2, 3, 7, 11, 15, and 19

Per Section 2.1.2.2 of the ISS, the data presented for the Phase 2 study in the ISS were through Week 37. Per Section 2.1 of the “abbreviated” study report, the protocol specified

b(4)

follow-up through Week 71; \_\_\_\_\_

\_\_\_\_\_ All subjects had completed treatment when the study was terminated. Of the 249 subjects randomized, 50 (20.1%) had their last follow-up visit at Week 71.

*Comment: Safety data collected from Weeks 37 to 71 appears to have been limited to serious adverse events, malignancies, adverse events related to the final blood draw, and pregnancies. Most subjects' final follow-up visits occurred at Weeks 48 or 59* \_\_\_\_\_

b(4)

There were no deaths in the multiple sclerosis development program.

One serious adverse event was reported an ustekinumab-treated subject in the Phase 1 study (through Week 16): breast cancer in a 53 year-old female 2 to 3 weeks after administration of study product. She had a history of breast cysts and benign breast biopsies, and her mother died of breast cancer at age 37.

In the Phase 2 study, 6 ustekinumab-treated subjects and one placebo-treated subject experienced serious adverse events through Week 37 of follow-up:

- 50 y/o female (180 mg): rotator cuff tear
- 43 y/o male (27 mg): squamous cell carcinoma of left tonsil (6 days after 8<sup>th</sup> dose)
- 44 y/o female (90 mg): depression, vomiting, dehydration
- 53 y/o female (27 mg): colon cancer (adenocarcinoma with one positive node ; 12 days after 7<sup>th</sup> dose)
- 32 y/o male (90 mg): dyspnea
- 47 y/o female (27 mg): exacerbation of pain (cervical and lumbosacral spine)
- 23y/o male (placebo): flank pain

An additional 6 subjects experienced adverse events through the Week 71 follow-up:

- 64 y/o female (90 mg): cerebrovascular accident (246 days after 7<sup>th</sup> dose)
- 39 y/o female (90 mg): "acute GI symptoms (nausea, stomach spasms)"
- 39 y/o female (180 mg): "potential steroid induced arrhythmia" (133 days after 8<sup>th</sup> dose)
- 44 y/o female (90 mg): worsening depression, vomiting, dehydration
- 40 y/o female (180 mg): hospitalization for removal of benign vocal cord polyp (149 days after 8<sup>th</sup> dose)
- 56 y/o female (90 mg): basal cell carcinoma (335 days after the 4<sup>th</sup> dose)

*Comment: A total of 4 malignancies were reported and all were reported as serious adverse events (above). Three of these subjects had factors which might have increased their risk for the type of malignancy seen:*

- *The subject with breast cancer's mother died young (37 years) of the same.*
- *The subject with tonsillar cancer had a history of smoking.*
- *The subject with colon cancer had a family history of this (also progressive anemia from one week after randomization suggests this disease process may have already been underway).*

*Curiously, the subject with basal cell carcinoma was "admitted to the hospital and underwent excision of a frontal skin tumor." The meaning of "frontal" is unclear, as is the reason (e.g. size) for removal requiring hospitalization.*

In the Phase 2 study, 170 (85.0%) subjects in the combined ustekinumab group and 38 (77.6%) subjects in the placebo treatment group had at least 1 adverse event. Infections and infestations was the most frequently reported category for all treatment groups: 48.0% for the combined ustekinumab group and 51.0% for the placebo group. As in the psoriasis ISS database, the most frequently reported events in each treatment group were upper respiratory tract infection and nasopharyngitis.

*Comment: While there were no serious infections, the proportions of subjects requiring oral or parenteral antibiotics were higher in ustekinumab treatment groups. The events for which there were more than one report in a treatment group are presented in the following table (Source: abbreviated study report):*

Attachment 4.10 Number of subjects with 1 or more treatment-emergent infections requiring oral or parenteral antimicrobial treatment by MedDRA system-organ class and preferred term; treated subjects

	Placebo	CNTO 1275			
		27 mg q4 weeks	90 mg q8 weeks	90 mg q4 weeks	180 mg q4 weeks
Subjects treated	49	51	47	52	50
Avg duration of follow-up (weeks)	36.6	36.4	36.8	34.5	36.1
Avg exposure (weeks)	19.2	19.1	18.7	18.1	18.9
Subjects with 1 or more infections requiring treatment	8 (16.3%)	19 (37.3%)	13 (27.7%)	12 (23.1%)	12 (24.0%)
<b>System-organ class/preferred term</b>					
Infections and infestations	8 (16.3%)	19 (37.3%)	13 (27.7%)	12 (23.1%)	10 (20.0%)
Upper respiratory tract infection	0 (0.0%)	3 (5.9%)	5 (10.6%)	3 (5.8%)	3 (6.0%)
Urinary tract infection	4 (8.2%)	2 (3.9%)	2 (4.3%)	2 (3.8%)	5 (10.0%)
Bronchitis	1 (2.0%)	2 (3.9%)	2 (4.3%)	0 (0.0%)	0 (0.0%)
Nasopharyngitis	0 (0.0%)	0 (0.0%)	2 (4.3%)	0 (0.0%)	2 (4.0%)
Sinusitis	2 (4.1%)	3 (5.9%)	0 (0.0%)	1 (1.9%)	0 (0.0%)
Pharyngitis	0 (0.0%)	2 (3.9%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Otitis media	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.8%)	0 (0.0%)
<b>Respiratory, thoracic and mediastinal disorders</b>					
Cough	0 (0.0%)	2 (3.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

“Cardiac disorders” through Week 37 in the Phase 2 trial are below (Source: Attachment 4.4 of the abbreviated study report):

	Placebo	27 mg q4 weeks	90 mg q8 weeks	90 mg q4 weeks	180 mg q4 weeks
Cardiac disorders	1 (2.0%)	4 (7.8%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Angina pectoris	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Palpitations	0 (0.0%)	2 (3.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bradycardia	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac flutter	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Decreased absolute lymphocytes was the hematology value that was most frequently out of range, and the percentage of subjects with this event was similar across treatment groups, with

18 (9.0%) of subjects in the combined ustekinumab treatment group and 6 (12.2%) of subjects in the placebo treatment group. Decreased calcium was the chemistry value that was most frequently out of range, and the number of subjects with this event was similar across treatment groups, with 6 (3.0%) subjects in the combined ustekinumab treatment group and 2 (4.1%) subjects in the placebo treatment group. There were no subjects with “markedly abnormal” (definition not found) post-baseline glucose levels.

#### **Conclusions on Safety Data in Other Indications**

The safety data from study of ustekinumab for other indications raised no new safety concerns. There were no reports of diverticulitis in any of the other development programs. There were no reports on infections by nontuberculous mycobacteria or salmonella. The occlusive vascular events seen in the psoriasis studies may be reflective of that population (and associated comorbidities/riks factors).

*Comment: It is noted that for psoriatic arthritis and Crohn’s disease subjects are required to have had an inadequate response, failed and/or had previous exposures to other therapies (e.g. anti-TNF agents), i.e. the product was evaluated as second-line therapy. The applicant proposes the product as first-line therapy for psoriasis.*

#### **7.4.2 Laboratory Findings**

The applicant applied the following criteria to make a determination that laboratory values were “markedly abnormal”:

<b>Table 1 Markedly Abnormal Criteria for Laboratory Values</b>	
<b>Hematology Test</b>	<b>Criteria for Markedly Abnormal Status</b>
RBC ( $\times 10^3/\mu\text{L}$ )	$< 3.0 \times 10^3$
Hemoglobin (g/dL)	Decrease $\geq 2$ AND Value $< 10.0$
Hematocrit (%)	Value $< 27$
Platelets ( $\times 10^3/\mu\text{L}$ )	Percent decrease $\geq 50$ AND Value $< 75$
WBC ( $\times 10^3/\mu\text{L}$ )	Value $< 2.0$ OR Value $> 20.0$
Eosinophils, absolute ( $\times 10^3/\mu\text{L}$ )	Percent increase $\geq 100$ AND Value $> 0.8$
Lymphocytes, absolute ( $\times 10^3/\mu\text{L}$ )	Percent decrease $\geq 33$ AND Value $< 1.0$
Neutrophils, absolute ( $\times 10^3/\mu\text{L}$ )	Percent decrease $\geq 33$ AND Value $< 1.5$
<b>Chemistry Test</b>	
<b>Criteria for Markedly Abnormal Status</b>	
BUN/Urea (mg/dL)	Percent increase $\geq 66$ AND Value $> 40$
Creatinine (mg/dL)	Percent increase $\geq 66$ AND Value $> 1.5$
Total bilirubin (mg/dL)	Percent increase $\geq 100$ AND Value $> 3.0$
Alkaline phosphatase (IU/L)	Percent increase $\geq 100$ AND Value $> 250$
ALT (IU/L)	Percent increase $\geq 100$ AND Value $\geq 150$
AST (IU/L)	Percent increase $\geq 100$ AND Value $> 150$
Sodium (mEq/L)	(Increase $\geq 10$ AND Value $\geq 150$ ) OR (Decrease $\geq 10$ AND Value $< 120$ )
Potassium (mEq/L)	(Increase $\geq 0.8$ AND Value $> 6.0$ ) OR (Decrease $\geq 0.8$ AND Value $< 3.0$ )
Glucose (mg/dL)	(Percent increase $\geq 50\%$ AND value $> 160$ ) OR (percent decrease $\geq 33\%$ AND value $< 55$ )
Chloride (mEq/L)	Value $< 85$ OR Value $> 120$
Calcium (mg/dL)	(Increase $\geq 2.0$ AND Value $> 11.5$ ) OR (Decrease $\geq 1.5$ AND Value $< 7.5$ )
Albumin (g/dL)	Decrease $\geq 1.0$ AND Value $< 3.0$
Total protein (g/dL)	Value $< 4.5$ OR Value $> 10.0$
<b>Note: Increases and decreases above are relative to the baseline value.</b>	

Source: Revised Statistical Analysis Plan for study T08

*Comment: These criteria are reasonable.*

The proportions of subjects with markedly abnormal laboratory values were generally comparable between placebo and ustekinumab treatment groups. No changes in routine laboratory parameters (hematology and chemistries) in Phase 1 raised safety concerns suggesting a treatment effect from ustekinumab, or an effect that should be specifically targeted for additional evaluation in later development.

#### Lymphocytes

There was no consistent effect on T-lymphocyte subsets in the Phase 1 studies.

Lymphocytes were further evaluated through Week 32 in the Phase 2 study (this study was 36 weeks in duration). Evaluations included absolute counts, CD3+, CD4+, CD8+ T cells, the CD4:CD8 ratio, CD19 B cells, and natural killer cells. No pattern suggesting ustekinumab effect emerged.

**Hematology**

**Through Week 12**

Rates of markedly abnormal changes in hematology laboratory values were generally similar between the treatment groups. Lymphocytes were the only parameter to qualify as markedly abnormal (decrease) in more than 1% of subjects: 3.2% of subjects in the placebo group, 2.4% in 45 mg group and 1.4% in the 90 mg group.

**Markedly Abnormal Hematology Values through Week 12 (Source Appendix B.75 ISS)**

	Placebo	45 mg	90 mg
Subjects treated	732	790	792
RBC (decreased)			
n	730	788	792
Subjects with any abnormal value	0 (0.0%)	1 (0.1%)	0 (0.0%)
Subjects with > 1 abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)
WBC (elevated)			
n	730	788	792
Subjects with any abnormal value	1 (0.1%)	0 (0.0%)	1 (0.1%)
Subjects with > 1 abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)
WBC (decreased)			
n	730	788	792
Subjects with any abnormal value	0 (0.0%)	1 (0.1%)	0 (0.0%)
Subjects with > 1 abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)

continued on next page

<b>Neutrophils, absolute (decreased)</b>			
n	730	788	792
Subjects with any abnormal value	1 (0.1%)	3 (0.4%)	1 (0.1%)
Subjects with > 1 abnormal value	0 (0.0%)	1 (0.1%)	0 (0.0%)
<b>Lymphocytes, absolute (decreased)</b>			
n	730	788	792
Subjects with any abnormal value	23 (3.2%)	19 (2.4%)	11 (1.4%)
Subjects with > 1 abnormal value	3 (0.4%)	5 (0.6%)	2 (0.3%)
<b>Eosinophils, absolute (elevated)</b>			
n	730	788	792
Subjects with any abnormal value	7 (1.0%)	5 (0.6%)	7 (0.9%)
Subjects with > 1 abnormal value	1 (0.1%)	2 (0.3%)	2 (0.3%)
<b>Platelets (decreased)</b>			
n	730	788	792
Subjects with any abnormal value	0 (0.0%)	0 (0.0%)	1 (0.1%)
Subjects with > 1 abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Neutrophils, absolute (decreased)</b>			
n	730	788	792
Subjects with any abnormal value	1 (0.1%)	3 (0.4%)	1 (0.1%)
Subjects with > 1 abnormal value	0 (0.0%)	1 (0.1%)	0 (0.0%)
<b>Lymphocytes, absolute (decreased)</b>			
n	730	788	792
Subjects with any abnormal value	23 (3.2%)	19 (2.4%)	11 (1.4%)
Subjects with > 1 abnormal value	3 (0.4%)	5 (0.6%)	2 (0.3%)
<b>Eosinophils, absolute (elevated)</b>			
n	730	788	792
Subjects with any abnormal value	7 (1.0%)	5 (0.6%)	7 (0.9%)
Subjects with > 1 abnormal value	1 (0.1%)	2 (0.3%)	2 (0.3%)
<b>Platelets (decreased)</b>			
n	730	788	792
Subjects with any abnormal value	0 (0.0%)	0 (0.0%)	1 (0.1%)
Subjects with > 1 abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)

Through the End of the Reporting Period

The most commonly reported markedly abnormal hematologic changes pertained to lymphocytes and eosinophils as presented in the following table:

**Markedly Abnormal Hematology Values Through the End of the Reporting Period**  
 (Source Appendix B.76 ISS)

	Placebo	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg
Subjects treated	732	320	364	790	792
<b>RBC (decreased)</b>					
n	730	319	364	788	792
Subjects with any abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Subjects with > 1 abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
<b>Hemoglobin (decreased)</b>					
n	730	319	364	788	792
Subjects with any abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
Subjects with > 1 abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)
<b>Hematocrit (decreased)</b>					
n	730	319	364	788	792
Subjects with any abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Subjects with > 1 abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
<b>WBC (elevated)</b>					
n	730	319	364	788	792
Subjects with any abnormal value	1 (0.1%)	0 (0.0%)	1 (0.3%)	1 (0.1%)	1 (0.1%)
Subjects with > 1 abnormal value	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
<b>WBC (decreased)</b>					
n	730	319	364	788	792
Subjects with any abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Subjects with > 1 abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Neutrophils, absolute (decreased)</b>					
n	730	319	364	788	792
Subjects with any abnormal value	1 (0.1%)	1 (0.3%)	1 (0.3%)	5 (0.6%)	5 (0.6%)
Subjects with > 1 abnormal value	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.5%)	1 (0.1%)
<b>Lymphocytes, absolute (decreased)</b>					
n	730	319	364	788	792
Subjects with any abnormal value	24 (3.3%)	7 (2.2%)	10 (2.7%)	39 (4.9%)	39 (4.9%)
Subjects with > 1 abnormal value	3 (0.4%)	1 (0.3%)	2 (0.5%)	10 (1.3%)	10 (1.3%)
<b>Eosinophils, absolute (elevated)</b>					
n	730	319	364	788	792
Subjects with any abnormal value	7 (1.0%)	5 (1.6%)	6 (1.6%)	13 (1.6%)	19 (2.4%)
Subjects with > 1 abnormal value	1 (0.1%)	0 (0.0%)	3 (0.8%)	5 (0.6%)	9 (1.1%)

*Comment: No hematologic events were reported as serious adverse events.*

**Clinical Chemistry**

Through Week 12

The only clinical chemistry value in which markedly abnormal changes were observed in more than 1% of ustekinumab subjects was elevated nonfasting glucose, which occurred in 6.7% of subjects in the placebo group, 5.5% in the 45 mg group and 5.1% in the 90 mg group. However, approximately twice as many subjects in both ustekinumab treatment groups had more than one markedly abnormal nonfasting glucose: 1.2% of subjects in the placebo group, 2.2% in the 45 mg group and 2.3% in the 90 mg group. The proportions in ustekinumab-treated subjects were similar between treatment groups.

**Markedly Abnormal Nonfasting Glucose through Week 12 (Source: Appendix B.77 ISS)**

	Placebo	45 mg	90 mg
Non-fasting glucose (elevated)			
n	730	788	792
Subjects with any abnormal value	49 (6.7%)	43 (5.5%)	40 (5.1%)
Subjects with > 1 abnormal value	9 (1.2%)	17 (2.2%)	18 (2.3%)

Baseline and Week 12 fasting glucose levels were evaluated to determine the rates meeting the World Health Organization diagnostic criterion for diabetes, i.e. a fasting glucose  $\geq 126$  mg/dL.

**Shift table of fasting glucose at Week 12; treated subjects in psoriasis Phase 3 (Source: Appendix B.7 ISS)**

	Placebo		45 mg		90 mg	
	Baseline Status		Baseline Status		Baseline Status	
	< 126 mg/dL	$\geq 126$ mg/dL	< 126 mg/dL	$\geq 126$ mg/dL	< 126 mg/dL	$\geq 126$ mg/dL
Baseline	540	59	572	52	573	52
Week 12						
n <sup>a</sup>	499	53	535	48	533	47
< 126 mg/dL	477 (95.6%)	13 (24.5%)	524 (97.9%)	17 (35.4%)	517 (97.0%)	11 (23.4%)
$\geq 126$ mg/dL <sup>b</sup>	22 (4.4%)	40 (75.5%)	11 (2.1%)	31 (64.6%)	16 (3.0%)	36 (76.6%)

<sup>a</sup> The denominator for the percentage is based on the number of subjects (n) with both a baseline and follow-up measurement within a treatment group and baseline status.

<sup>b</sup> Based on diagnostic criteria from *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications: Report of a WHO Consultation. Part I: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Organization, 1999.

Among subjects with a baseline fasting glucose < 126 mg/dL, the rates of subjects who developed elevated fasting glucose  $\geq 126$  mg/dL at Week 12 were comparable in all groups: 4.4% of subjects in the placebo group, 2.1% in the 45 mg group and 3.0% in the 90 mg groups, respectively. Among subjects with a baseline fasting glucose  $\geq 126$  mg/dL, the rates of subjects who had fasting glucose < 126 mg/dL at Week 12 were comparable between the placebo and 90 mg groups at 24.5% and 23.4%, respectively and highest in the 45 mg group at 35.4%.

Through the End of the Reporting Period

Again, the most frequently reported markedly abnormal clinical chemistry value through the end of the reporting period was an increase in nonfasting glucose levels. No dose

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

response was observed, and comparable proportions of subjects in the 45 mg and 90 mg groups and the placebo → 45 mg and placebo → 90 mg had markedly abnormal changes in nonfasting glucose.

**Markedly Abnormal Nonfasting Glucose through the End of the Reporting Period (Source: Appendix B.79 ISS)**

	Placebo	CNTO 1275			
		Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg
Non-fasting glucose (elevated)					
n	730	319	364	788	792
Subjects with any abnormal value	51 (7.0%)	38 (11.9%)	35 (9.6%)	89 (11.3%)	93 (11.7%)
Subjects with > 1 abnormal value	11 (1.5%)	21 (6.6%)	19 (5.2%)	51 (6.5%)	46 (5.8%)

**Hemoglobin A1c**

Hemoglobin A1c levels were obtained at baseline and every 12 weeks in the Phase 3 psoriasis studies to evaluate the impact of ustekinumab on glucose homeostasis.

**Summary of hemoglobin A1c (Source: Appendix B.80 of ISS)**

	Placebo	CNTO 1275		
		45 mg	90 mg	Combined
Subjects treated	665	664	666	1330
Hemoglobin A1c (%)				
Baseline				
n	654	656	660	1316
Mean ± SD	5.86 ± 0.990	5.86 ± 1.076	5.88 ± 0.984	5.87 ± 1.030
Median	5.60	5.60	5.70	5.60
IQ range	(5.30, 6.00)	(5.40, 6.00)	(5.40, 6.00)	(5.40, 6.00)
Range	(3.7, 12.7)	(3.8, 16.1)	(4.2, 13.1)	(3.8, 16.1)
Week 12				
n	649	652	649	1301
Mean ± SD	5.89 ± 0.908	5.92 ± 1.047	5.91 ± 0.932	5.91 ± 0.991
Median	5.70	5.70	5.70	5.70
IQ range	(5.40, 6.10)	(5.40, 6.00)	(5.40, 6.00)	(5.40, 6.00)
Range	(3.7, 12.2)	(3.9, 15.7)	(3.8, 12.4)	(3.8, 15.7)
Increase in hemoglobin A1c (%) from baseline at Week 12				
n	638	646	646	1292
Subjects with increase ≥ 1%	5 (0.8%)	10 (1.5%)	8 (1.2%)	18 (1.4%)
Subjects with increase ≥ 2%	1 (0.2%)	2 (0.3%)	2 (0.3%)	4 (0.3%)

The levels remained stable in all groups during the placebo-controlled period and were comparable between the placebo and ustekinumab groups.

*Comment: These analyses suggest no adverse impact of ustekinumab on glucose homeostasis.*

### D-dimer

D-dimer levels were obtained at baseline and Week 12 to evaluate the impact of ustekinumab on occult thrombosis.

Shift table of D-dimer at Week 12; treated subjects in psoriasis Phase 3 (Appendix B.81 ISS)

	Placebo		45 mg		90 mg	
	Baseline Status		Baseline Status		Baseline Status	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Baseline	531	110	550	96	557	95
Week 12						
n <sup>a</sup>	515	104	536	92	538	92
Normal <sup>b</sup>	469 (91.1%)	34 (32.7%)	498 (92.9%)	34 (37.0%)	498 (92.6%)	43 (46.7%)
Abnormal	46 (8.9%)	70 (67.3%)	38 (7.1%)	58 (63.0%)	40 (7.4%)	49 (53.3%)

<sup>a</sup> The denominator for the percentage is based on the number of subjects (n) with both a baseline and follow-up measurement within a treatment group and baseline status.

<sup>b</sup> The reference range is defined as 0 to ≤ 316 ng/mL.

Among subjects with a normal D-dimer at baseline, most (> 90%) had normal levels at Week 12, and the rates of subjects who developed an abnormal D-dimer at Week 12 were highest in the placebo group. Among subjects with an abnormal baseline D-dimer, the rates of subjects who had a normal D-dimer at Week 12 were highest in the 90 mg group.

*Comment: The results suggest that ustekinumab does not adversely impact D-dimer levels.*

### C-reactive Protein

C-reactive protein (CRP) levels were obtained at baseline and Week 12 to evaluate the impact of ustekinumab on cardiovascular risk.

Shift table of CRP at Week 12; treated subjects in psoriasis Phase 3 (Appendix B.82)

	Placebo		45 mg		90 mg	
	Baseline Status		Baseline Status		Baseline Status	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Baseline	452	200	472	189	462	199
Week 12						
n <sup>a</sup>	440	194	465	187	454	192
Normal <sup>b</sup>	410 (93.2%)	54 (27.8%)	437 (94.0%)	82 (43.9%)	419 (92.3%)	85 (44.3%)
Abnormal	30 (6.8%)	140 (72.2%)	28 (6.0%)	105 (56.1%)	35 (7.7%)	107 (55.7%)

<sup>a</sup> The denominator for the percentage is based on the number of subjects (n) with both a baseline and follow-up measurement within a treatment group and baseline status.

Among subjects with a normal CRP at baseline, most (> 90%) had normal levels at Week 12, and the rates of subjects who developed abnormal levels at Week 12 were highest in the 90 mg group and lowest in the 45 mg group. Among subjects who had an abnormal baseline CRP, more subjects in ustekinumab treatment groups had normal CRP at Week 12 than did in the placebo group. Of subjects who had abnormal levels at baseline, more subjects in ustekinumab treatment groups had normal CRP at Week 12 than did in the placebo group.

*Comment: These results suggest that ustekinumab does not increase CRP levels. It might have been interesting to see how d-dimer and CRP levels did beyond Week 12.*

### 7.4.3 Vital Signs

Blood pressure, pulse, and temperature were measured in the Phase 1 psoriasis studies. No vital sign measurement was assessed as being clinically significant by the investigator in study C0379T01. There were no substantial differences in the median values for any of the vital sign measurements at any time point between subjects who received placebo and those who received ustekinumab in study C0379T02. One ustekinumab subject had “markedly abnormal high systolic blood pressure” (defined as  $\geq 180$  mmHg and  $\geq 20$  mmHg increase from baseline): this subject’s systolic blood pressure was 180 mm Hg 4 weeks post-dosing.

Vital signs were measured for safety purposes in studies T04 and T09; however, no formal analyses were done on these data. There were no clinically notable signals of vital sign abnormalities.

Weight and blood pressure were measured in T08. Weights remained stable over time in all treatment groups, and ustekinumab had no apparent impact on blood pressure.

### 7.4.4 Electrocardiograms (ECGs)

ECG measurements were performed in all the Phase 1 studies (2 in psoriasis; 1 in MS) and a subset of subjects in the Phase 2 psoriasis study. The applicant reported no clinically important ECG changes in either of the Phase 1 studies in the psoriasis development program (single dose studies). Two subjects (females) in one of these studies (C0379T02) had “markedly abnormal” post-baseline QTc intervals (defined as  $> 470$  msec for females, or  $> 60$  msec increase from baseline for either gender; ECGs were performed at screening, baseline, pre-injection, 24 hours after administration of study agent, and at Weeks 16 and 24):

- Subject #001-001 (0.3mg/kg group) had a QTc interval of 450 msec at screening and an abnormal measurement of 473 msec at Week 24.
- Subject #003-003 (0.75 mg/kg) had a pre-injection QTc of 470 msec and abnormal measurement of 471 at Week 16; the interval was 465 msec at Week 24.

*Comment: The reviewer notes that one subject was at the threshold of “abnormal” pre-injection (470 msec), and her “abnormal” reading was 471, i.e. the minimum value necessary to be considered abnormal (defined as  $> 470$  msec for females).*

In the Phase 2 study (T04), ECGs were done at screening until the first 39 subjects were randomized. Post-baseline ECGs were done at Week 32. Definitions of normal are presented in the following table:

Definitions of normal ranges for ECG test values (Source: study report for T04)

ECG Test	Values Considered Normal
Heart rate (beats/minute)	60 to 100
QRS duration (sec)	0.05 to 0.10
PR interval (sec)	0.12 to 0.20
QT interval (msec)	$< 471$
QTc (msec)	$< 471$
Maximum ST elevation (mm)	$\leq 1.0$ mm (see Section 7.2)

A total of 10 subjects in study T04 had at least 1 abnormal post-baseline ECG value:

- 3 in the placebo group: abnormally high ventricular rate and abnormally “high” QRS duration (2 subjects)
- 3 in the 90 mg single dose group: abnormally high ventricular rate, abnormally low ventricular rate/abnormally “high” PR interval and QRS duration and abnormally “high” QRS duration
- 2 in the 45 mg (weekly x 4) group: abnormally low ventricular rate and abnormally “high” QRS duration
- 2 in the 90 mg (weekly x 4) group: abnormally high PR interval and QRS duration; abnormally QRS duration

The applicant concluded that the abnormal post-baseline ECG intervals were not substantially different from values at screening or baseline, and no safety signal emerged. No pattern emerged that was associated with increasing dose.

*Comment: The reviewer agrees with these conclusions.*

In the MS study, 12 subjects had ECG assessments that were abnormal: 2 in the placebo group, 2 in the 0.3 mg/kg ustekinumab group, 1 in the 0.75 mg/kg group, 3 in the 1.5 mg/kg group, and 4 in the 3.0 mg/kg group. The most common abnormal findings (and the only ones presented in the discussion in Section 8.5.2 of the study report were) sinus bradycardia [7 reports (5, 1.5 mg/kg ; 2, 3.0 mg/kg)] and sinus arrhythmia [3 reports (1 each: placebo, 0.3 mg/kg, and 0.75 mg/kg)]. However, per the study report, “no changes from baseline in ECG assessments were recorded as (adverse events) for any subject,” and no ECG changes were considered by investigators to be clinically significant.

*Comment: Prior to submission of the marketing application, the DDDP had obtained a consult from the QT-IRT team regarding recommendations for a thorough clinical QT study. The consult reply included the following comments:*

*“In our opinion, monoclonal antibodies do not need to be evaluated in a thorough clinical QT study because:*

- a. as large molecules, monoclonal antibodies cannot access the hERG pore via the intracellular side, which is the target site for most small-molecule QT-prolonging drugs; and*
- b. monoclonal antibodies can have off-target cardiac effects but QT prolongation has not been observed.”*

*Thus, a thorough QT study was not requested of the applicant.*

#### 7.4.5 Special Safety Studies

No special safety studies were done.

### 7.4.6 Immunogenicity

The applicant reports a generally low incidence of antibodies to ustekinumab at approximately 4%. However, the true incidence of antibody positivity is unclear as testing was done at time points when ustekinumab may have still been present in the serum (i.e. at follow-up visit for assessment and maintenance treatment), and the presence of ustekinumab in the serum interferes with the antibody assay (see Section 4.1).

**Immunogenicity Results Study T08 (Source: Attachments 2.9 and 2.10 of study report for T08)**

	Placebo to 45 mg	Placebo to 90 mg	45 mg	90 mg
Subjects ≤100 kg	78	79	168	163
Subjects with appropriate samples	77	78	167	160
Positive at any time	3 (3.9%)	3 (3.8%)	2 (1.2%)	3 (1.9%)
Negative after last treatment	43 (55.8%)	50 (64.1%)	77 (46.1%)	50 (31.3%)
Inconclusive after last treatment	31 (40.3%)	25 (32.1%)	88 (52.7%)	107 (66.9%)
Subjects > 100 kg	45	41	87	92
Subjects with appropriate samples	44	39	87	91
Positive at any time	3 (6.8%)	6 (15.4%)	16 (18.4%)	2 (2.2%)
Negative after last treatment	27 (61.4%)	24 (61.5%)	45 (51.7%)	35 (38.5%)
Inconclusive after last treatment	14 (31.8%)	9 (23.1%)	26 (29.9%)	54 (59.3%)

**Immunogenicity Results Study T09 (Source: Attachments 2.5 and 2.6 of study report for T09)**

	Placebo to 45 mg	Placebo to 90 mg	45 mg	90 mg
Subjects ≤100 kg	135	140	297	289
Subjects with appropriate samples	133	140	298	287
Positive at any time	5 (3.8%)	0 (0.0%)	6 (2.0%)	4 (1.4%)
Negative after last treatment	8 (6.0%)	6 (4.3%)	25 (8.5%)	9 (3.1%)
Inconclusive after last treatment	120 (90.2%)	134 (95.7%)	264 (89.5%)	274 (95.5%)
Subjects > 100 kg	62	55	112	121
Subjects with appropriate samples	59	54	110	119
Positive at any time	0 (0.0%)	1 (1.9%)	12 (10.9%)	5 (4.2%)
Negative after last treatment	8 (13.6%)	8 (14.8%)	16 (14.5%)	10 (8.4%)
Inconclusive after last treatment	51 (86.4%)	45 (83.3%)	82 (74.5%)	104 (87.4%)

**Comment:** "Inconclusive" means that subjects had measurable drug levels. The documented number of antibody-positive subjects is relatively low in T08 in all categories; however, the number of subjects who had inconclusive status is relatively high in all categories. A similar but more pronounced pattern was seen in study T09, with relatively low numbers of documented antibody positive subjects; however, most subjects in this study had antibody status that was inconclusive.

The results reveal a possible association between subjects heavier than 100 kg and antibody positivity, and a possible association between 45mg dosing and antibody positivity.

### Impact on Efficacy

In study T08, of 162 subjects who were long-term PASI 75 responders and were randomized to maintenance therapy at Week 40 (subjects who had received ustekinumab from Week 0 and had maintained a PASI 75 response), 3 (1.9%) were antibody positive, 36 (22.2%) were antibody negative, and 123 (75.9%) had inconclusive antibody status.

In study T09, the applicant evaluated the impact of antibodies to ustekinumab on efficacy by evaluating the PASI 75 and PASI 50 responses according to antibody status at Week 28 for subjects randomized to active treatment at Week 0. Per the study report for T09 (Figure 22) of 17 antibody-positive subjects in the 45 mg group, approximately 12 % had a PASI 75 at Week 28 and 71% had a PASI 50. In the 90 mg group, of 9 antibody-positive subjects, approximately 33% had a PASI 75 at Week 28 and 67% had a PASI 50.

*Comment: The results presented from study T08 represent efficacy outcomes for 3 documented antibody-positive subjects, and this number is far too few to permit any conclusions regarding the impact of antibodies on efficacy outcomes in this study. The results presented from study T09 represent efficacy outcomes for 26 subjects, and most did not achieve the primary measure of efficacy of PASI 75 (most did achieve some measure of response as reflected in the percentage who achieved PASI 50). These limited data suggest decreased efficacy in antibody-positive subjects; however, the data are inadequate to rely on for definitive conclusions regarding the impact of antibodies on efficacy outcomes. As a general principle, decreased efficacy may not necessarily translate into unacceptable results in treatment of psoriasis.*

### Safety

The safety of the product in antibody-positive subjects is based on limited data. Adverse events in documented antibody-positive subjects were all injection site reactions, and consistent with the overall safety database, the most commonly reported injection site reaction was erythema. There was one report of injection site urticaria. From review of the “all adverse events” tables, there were a few single reports of adverse events of possible immunologic origin, e.g. anaphylactic reaction, but these events occurred in subjects of uncertain antibody status and revealed no pattern of occurrence.

*Comment: Possible clarifying investigations of immunogenicity of ustekinumab include a clinical trial in which the testing is done at time points that have allowed for clearance of ustekinumab, or development of an assay with which the presence of ustekinumab does not interfere.*

## **7.5 Other Safety Explorations**

### **7.5.1 Dose Dependency for Adverse Events**

The discussion of adverse events includes comparisons of 45 mg to 90 mg.

### 7.5.2 Time Dependency for Adverse Events

No apparent time dependency for adverse events was identified through the end of reporting period; however, the duration of follow-up is insufficiently long to speak to time dependency for malignancies.

### 7.5.3 Drug-Demographic Interactions

The rates of adverse events, serious adverse events, and adverse events leading to study agent discontinuation were analyzed in subpopulations based on age, sex, race, and geographic region using safety data pooled across the Phase 2 and 3 psoriasis studies. The ISS did not present the specific adverse events (e.g. nasopharyngitis); only the proportions of subjects in each subgroup who had any adverse event were presented.

*Comment: The reviewer could not find a presentation of specific adverse events in the study reports for the Phase 3 studies.*

#### Age

The proportion of subjects who were < 45 years (n=1,061) who had at least 1 adverse event during the placebo-controlled period was similar between treatment groups: 53.7% in the placebo group, 57.0% in the 45 mg group and 55.4% in the 90 mg group. In this age group, the proportion of subjects who had least 1 serious adverse event was similar between the placebo and 90 mg groups treatment groups and highest in the 45 mg group: 0.9% in the placebo group, 2.4% in the 45 mg group and 0.9% in the 90 mg group.

The proportion of subjects who were ≥45 to < 65 years (n=1,119) who had least 1 adverse event during the placebo-controlled period was similar between the placebo and 90 mg groups treatment groups and highest in the 45 mg group: 47.8% in the placebo group, 56.5%.4% in the 45 mg group and 48.4% in the 90 mg group. In this age group, the proportion of subjects who had least 1 serious adverse event was similar between the placebo and 90 mg groups treatment groups and lowest in the 45 mg group: 2.0% in the placebo group, 0.8% in the 45 mg group and 1.8% in the 90 mg group.

The proportion of subjects who were ≥65 years (n=134) who had least 1 adverse event during the placebo-controlled period was highest in the 45 mg group, and both the 45 mg and 90 mg group had higher proportions than did placebo: 45.8% in the placebo group, 73.2% in the 45 mg group and 51.8% in the 90 mg group. In this age group, the proportion of subjects who had least 1 serious adverse event was similar between the 45 mg and 90 mg b groups (1 subject each) and lowest in placebo (none): 0.0% in the placebo group, 2.4% in the 45 mg group and 2.2% in the 90 mg group.

*Comment: Comparing age categories, the proportion of subjects who had at least 1 adverse event during the placebo-controlled period was generally similar except for subjects ≥65 years, 73.2% of whom in the 45 mg group reported at least 1 adverse event. No pattern was identified to suggest an age effect.*

#### Sex

The proportion of females (n=722) who had least 1 adverse event during the placebo-controlled period was similar between the placebo and 90 mg treatment groups and highest in

the 45 mg group: 59.0% in the placebo group, 66.0% in the 45 mg group and 48.1% in the 90 mg group. In each treatment group, more females had at least 1 adverse event than did males (see next paragraph). The proportion of females who experienced at least 1 serious adverse event was highest in the placebo group (1.8%) compared to the 45 mg group (0.4%) and 90 mg group (0.8%).

The proportion of males (n=1,592) who had least 1 adverse event during the placebo-controlled period was similar between the placebo and 90 mg groups treatment groups and highest in the 45 mg group: 46.8% in the placebo group, 53.6% in the 45 mg group and 59.4% in the 90 mg group. The proportion of males who experienced at least 1 serious adverse event was highest in the 45 mg group (2.2%), but generally similar between all treatment groups, the placebo group (1.2%) and 90 mg group (1.7%).

### Race

The proportion of adverse events was compared between Caucasians, Blacks, Asians, and "Other."

The proportion of Caucasians (n=2141) who had least 1 adverse event during the placebo-controlled period was highest in the 45 mg group (58.5%) and similar between the placebo and 90 mg groups (50.1% and 51.2%, respectively). The proportion of Caucasians who had least 1 serious adverse event during the placebo-controlled period was similar between all groups 1.2% to 1.8%).

The proportion of Blacks (n=47) who had least 1 adverse event during the placebo-controlled period was distinctly higher the placebo group (64.3%) compared to the 45 mg and 90 mg groups (42.1% and 42.9%, respectively). One Black subject had at least 1 serious adverse event during the placebo-controlled period, and that subject was in the placebo group (7.1%)

The proportion of Asians (n=79) who had least 1 adverse event during the placebo-controlled period was highest in the 90 mg group (53.6%) and similar between the placebo and 45 mg groups (46.7% and 47.6%, respectively). No Asian subject experienced a serious adverse event.

The proportion of "Other" subjects (n= 47) who had least 1 adverse event during the placebo-controlled period was highest in the 90 mg group (73.7%), lowest in the 45 mg group (47.1%); it was 63.6% in the placebo group. Two subjects in this group experienced serious adverse events, and both were in the 90 mg group (10.5%).

*Comment: Generally, in all subgroups (and categories within each subgroup), through the end of the reporting period, the proportions of subjects who had at least 1 adverse event were highest in the 45 mg and 90 mg groups compared to the placebo → 45 mg and placebo → 90 mg. Generally, the proportions were similar between the 45 mg and 90 mg groups and generally similar between placebo → 45 mg and placebo → 90 mg. Trends towards similar patterns were seen with serious adverse events.*

Weight

Number of subjects with 1 or more treatment-emergent adverse events, serious adverse events, or adverse events leading to discontinuation through Week 12 by body weight ( $\leq 100$  kg,  $> 100$  kg) at Week 0; treated subjects in psoriasis Phase 2 and Phase 3  
 (Appendix B.87 of ISS)

	Placebo	CNTO 1275		
		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%)

**Number of subjects with 1 or more treatment-emergent adverse events, serious adverse events, or adverse events leading to discontinuation through the end of the reporting period by body weight ( $\leq 100$  kg,  $> 100$  kg) at Week 0; treated subjects in psoriasis Phase 2 and Phase 3 (Appendix B.88 ISS)**

	Placebo	CNTO 1275				Combined
		Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg	
Subjects treated	732	320	364	790	792	2266
Subjects with weight $\leq 100$ kg						
n	502	213	254	556	542	1565
Avg duration of follow-up (weeks)	12.9	26.3	24.9	36.7	36.6	33.3
Subjects with 1 or more adverse events	257 (51.2%)	132 (62.0%)	153 (60.2%)	443 (79.7%)	414 (76.4%)	1142 (73.0%)
Subjects with 1 or more serious adverse events	8 (1.6%)	5 (2.3%)	4 (1.6%)	21 (3.8%)	18 (3.3%)	48 (3.1%)
Subjects who discontinued study because of 1 or more adverse events	8 (1.6%)	2 (0.9%)	2 (0.8%)	16 (2.9%)	15 (2.8%)	35 (2.2%)
Subjects with weight $> 100$ kg						
n	230	107	110	234	249	700
Avg duration of follow-up (weeks)	13.0	26.6	25.8	37.9	38.5	34.5
Subjects with 1 or more adverse events	115 (50.0%)	78 (72.9%)	74 (67.3%)	183 (78.2%)	199 (79.9%)	534 (76.3%)
Subjects with 1 or more serious adverse events	3 (1.3%)	5 (4.7%)	2 (1.8%)	11 (4.7%)	9 (3.6%)	27 (3.9%)
Subjects who discontinued study because of 1 or more adverse events	7 (3.0%)	4 (3.7%)	1 (0.9%)	8 (3.4%)	9 (3.6%)	22 (3.1%)

*Comment: The specific adverse events were not presented in the ISS. However, in the study reports for T08 and T09, the most commonly reported adverse events for weight categories were nasopharyngitis and upper respiratory tract infection. There was no pattern of adverse events evidenced when weight/dose were considered. The adverse event profiles were similar in both studies, despite subjects having received more study agent in T08 than T09. The adverse event profile was generally similar to that of the overall safety database. Lower weight subjects generally appear to have tolerated 90mg dosing at least as well as 45mg dosing. Generally, it appears that subjects  $> 100$  kg had more serious adverse events, and one possible explanation is that some heavier subjects might be at increased risk for serious adverse events because of comorbidities.*

#### 7.5.4 Drug-Disease Interactions

This section will discuss rebound and atopy.

*Comment: The applicant is evaluating their product for treatment of psoriatic arthritis, and to the reviewer's awareness, there has been no suggestion to date that their product worsens the arthritis in that program.*

#### Rebound

Rebound was defined if one of the following occurred within 3 months of stopping ustekinumab:

- PASI of 125% of baseline (i.e. a worsening of PASI by 25% or greater from baseline)
- new generalized pustular, erythrodermic or more inflammatory psoriasis

**Comment:** *It is not clear that assessment for rebound at this time point is the most appropriate for ustekinumab (because of its long half life, it may not have fully cleared from the serum). This approach could make for false reassurances that rebound is not seen with the product.*

Ten subjects had a PASI of  $\geq 125\%$  of the baseline within 3 months of stopping ustekinumab, 7 of whom had been non-responders. One subject was a treatment success who experienced rebound approximately 12 weeks after the last dose. Six subjects who experienced rebound were in the 45 mg group and four in the 90 mg. Per Appendix B.68, 7 subjects experienced rebound within one month of their last dose of ustekinumab.

**Comment:** *By the definitions applied in the ISS, the results suggests that the occurrence of rebound may represent inherent worsening of disease that might have been unrelated to ustekinumab, since rebound most often occurred in non-responders.*

#### Atopy

The applicant's product has the theoretical potential to exacerbate atopic conditions because of theoretical potential to "block differentiation of Th1 cells leading to greater polarization of immune responses towards a Th2 phenotype." The following table presents the percentages of subjects with conditions in the atopic diathesis enrolled in the Phase 3 studies.

**Atopy in the Phase 3 Studies (Source Appendix B.7 of ISS)**

Condition	Study T08 n=766	Study T09 n=1230
Asthma	68 (8.9%)	92 (7.5%)
Seasonal allergy/hayfever	194 (25.3%)	256 (20.8%)
Atopic dermatitis	6 (0.8%)	17 (1.4%)

There was one serious adverse event of worsening asthma, and it occurred in a subject who received placebo treatment (29 year-old female who had been smoking the night prior to the onset of exacerbation). No subjects discontinued the agent due to asthma.

In the ISS database, rates of events that the reviewer considered were (or might have been) reflective of atopy were similar between the three treatment groups during the placebo-controlled period, i.e. through Week 12. Those events (listed by preferred term; source: Appendix B.9) included nasopharyngitis, sinusitis, pharyngitis, bronchitis, rhinitis, sinus congestion, nasal congestion, allergic rhinitis, asthma, postnasal drip, and rhinorrhea. There were single reports of other events (e.g. allergic sinusitis, sneezing, bronchospasm, wheezing), and no pattern was identified in regard to correlation with treatment group. Asthma was reported in one subject (0.1%) in the placebo group and 4 (0.5%) in the 90 mg group. Atopic dermatitis was reported in one subject during this period, and that subject was in the placebo group. Events that occurred in  $\geq 1\%$  of ustekinumab-treated subjects are listed in the table of adverse events.

Through the end of the reporting period, rates of events were somewhat higher in ustekinumab-treated subjects; however, this might be explained by the longer follow-up for these subjects (compared to 12 weeks of follow-up for placebo-treated subjects).

### 7.5.5 Drug-Drug Interactions

The applicant did not perform formal drug-drug interaction studies. However, such will be requested as a Phase 4 commitment for reasons presented below from the Clinical Pharmacology review (by Dr. Abimbola Adebowale)

“Cytokines such as interleukin (IL)-2, IL-6 and IL-10 are known to downregulate the expression of cytochrome P450 enzymes (CYP) in humans and inhibit the metabolism of CYP substrates. On the contrary, cytokine antagonists such as basiliximab (anti-IL-2 receptor antibody)...are known to reverse the effect of the cytokines on CYP substrates, resulting in a "normalization" of CYP regulation. As a disease state, psoriatic patients have elevated cytokine levels. Ustekinumab as an IL-12/IL-23 antagonist has the potential to reverse any IL-12/IL-23 cytokine mediated CYP suppression. Thus in psoriasis patients who have been stabilized on drugs with CYP mediated metabolism, ustekinumab has the potential, through this normalization of CYP activity to require dose adjustment.”

*Comment: The Clinical Pharmacology reviewer proposes the following wording for the Phase 4 commitment: “Please conduct an in vitro study or studies to determine whether IL-12 and/or IL-23 modulate CYP enzyme expression and whether ustekinumab is able to reverse the effects of IL-12/IL-23 on CYP expression (e.g., in vitro hepatocyte study). An alternative in vivo approach would be to determine the potential of ustekinumab for the alteration of CYP substrate metabolism in psoriasis patients (e.g., a cocktail study with CYP probe drugs).”*

## 7.6 Additional Safety Explorations

### 7.6.1 Human Carcinogenicity

The theoretical risk of malignancy based on animal data from studies not conducted with the applicant’s product has been previously discussed. While malignancies were reported in the development program, in the reviewer’s opinion, it is not likely that the study product was causative (given the time points at which malignancies developed which would not be reflective of the generally long latency periods for malignancies). However, it is unclear to what extent the immunosuppression induced by the applicant’s product might have contributed to aggressive behavior of tumors (e.g. metastasis). No pattern to the types of malignancies was observed.

### 7.6.2 Human Reproduction and Pregnancy Data

A total of 17 pregnancies were reported in the psoriasis development program prior to data-lock: 10 in study subjects and 7 in partners of study subjects. The outcomes are reported as follows:

- 5 pregnancies resulted in healthy babies
- 2 resulted in spontaneous abortions
- 5 resulted in elective abortion
- 5 were continuing normally at the time of data-lock

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

An additional 8 pregnancies were reported after data-lock: 3 in study subjects and 5 in partners of study subjects.

The table below presents additional information regarding the pregnancies that occurred in study subjects, i.e. females enrolled in the studies who were exposed to study product.

**Pregnancy outcomes for study subjects (Sources: study reports for T04, T08 and T09)**

Subject; age	Dosage group x #of doses	trimester	outcome
T04-003-023; 37y/o	90 x 1	first	healthy girl
T08-031-002;	90 x 3	first	spontaneous abortion 51 days after reporting pregnancy
T08-009-021; age?	90 x 2	not clear	unknown; lost-to-followup
T08-022-002; 31 y/o	45 x 2	first	elective abortion
T08-021-007; age?	45 x 4	?	ongoing
T08-009-002; age?	90 x 6	?	ongoing
T08-113-009; age?	90 x ?	?	elective abortion
T09-007-009; 22 y/o	45 x 3	first	elective abortion
T09-019-019; 35 y/o	90 x 2	?	elective abortion
T09-117-013; 22 y/o	90 x 1	first	elective abortion
*T08-113-009; ?	90 x ?	?	elective abortion
*T09-015-033; ?	90 mg	?	elective abortion
*T09-104-012	90 mg	?	ongoing at time of database lock

"ongoing" = pregnancy was reported as continuing at the time the study report was drafted.

\*after database lock

*Comment: No deductions can be made regarding any potential impact of ustekinumab on pregnancies that occurred in 13 females who were exposed to study product as 7 had elective abortions, one had a spontaneous abortion and one was lost to follow-up. However, there was no signal in the animal studies.*

Outcomes for partner pregnancies, as described in the study reports are presented below:

- T04-037-002: healthy girl
- T04-003-001: full-term boy
- T08-032-018: ongoing
- T09-005-043: spontaneous abortion
- T09-002-002: healthy boy
- T09-006-004: ongoing
- T09-404-025: healthy baby (gender not specified)

The Safety Update included reports of 19 pregnancies that occurred in ustekinumab treated subjects or their partners:

**Appendix B.59 Summary of pregnancies reported after initial database locks through 31 Dec 2007 in PHOENIX 1 and PHOENIX 2 and through Week 12 database lock in ACCEPT**

Subject No.	Event	Date of Event	Dose Group	Outcome
C0743T08-106-002 <sup>a</sup>	Partner pregnancy	April 2007	CNTO 1275 90 mg	Subject discontinued the study and the outcome of the pregnancy is unknown <sup>a</sup>
C0743T08-113-009 <sup>a</sup>	Pregnancy	January 2007	CNTO 1275 90 mg	Elective abortion on [redacted]
C0743T08-009-003 <sup>a</sup>	Partner Pregnancy	11 Sep 2007	Placebo to CNTO 1275 45mg	Pregnancy continuing. Expected delivery date of May 2008.
C0743T08-009-027 <sup>a</sup>	Pregnancy	28 Nov 2007	CNTO 1275 45mg	Pregnancy continuing. Expected delivery date of August 2008.
C0743T08-025-015 <sup>a</sup>	Pregnancy	12 Dec 2007	CNTO 1275 45mg	Elective abortion on [redacted]
C0743T08-109-014 <sup>a</sup>	Partner Pregnancy	30 Oct 2007	CNTO 1275 45mg	Pregnancy continuing. expected delivery date of May 2008.
C0743T08-114-004 <sup>a</sup>	Partner Pregnancy	28 Nov 2007	CNTO 1275 45mg	Pregnancy continuing. Expected delivery date of July 2008.
C0743T08-018-017 <sup>a</sup>	Pregnancy	30 Oct 2007	CNTO 1275 45mg	Pregnancy continuing. Expected delivery date of June 2008.
C0743T08-031-015 <sup>a</sup>	Partner Pregnancy	May 2007	CNTO 1275 45mg	Pregnancy continuing. Expected delivery date of March 2008.
C0743T08-202-002 <sup>a</sup>	Partner Pregnancy	01 Mar 2007	Placebo to CNTO 1275 90 mg	Unknown.
C0743T09-600-002 <sup>b</sup>	Partner pregnancy	December 2006	CNTO 1275 90 mg	Subject had an abortion in [redacted] because the baby was not growing properly.
C0743T09-124-007 <sup>b</sup>	Partner pregnancy	November 2006	Placebo to CNTO 1275 45 mg	Healthy male infant delivered on [redacted]
C0743T09-014-007 <sup>b</sup>	Partner pregnancy	May 2007	CNTO 1275 45 mg	Pregnancy continuing. Expected delivery date December 2007.
C0743T09-015-033 <sup>b</sup>	Pregnancy	April 2007	CNTO 1275 90 mg	Elective abortion in [redacted]
C0743T09-104-012 <sup>b</sup>	Pregnancy	March 2007	CNTO 1275 90 mg	Subject lost to follow-up.
C0743T09-124-027 <sup>b</sup>	Partner Pregnancy	December 2006	CNTO 1275 45 mg	Healthy male infant delivered on [redacted]
C0743T09-119-014 <sup>b</sup>	Pregnancy	13 Aug 2007	CNTO 1275 45mg	Subject had a spontaneous abortion on [redacted]
C0743T09-013-019 <sup>b</sup>	Partner Pregnancy	20 Nov 2006	CNTO 1275 45mg	Healthy female infant delivered on [redacted]
C0743T09-015-028 <sup>b</sup>	Pregnancy	03 Oct 2007	CNTO 1275 90 mg	Pregnancy continuing.

b(6)

b(6)

With regard to post-marketing assessments of pregnancy exposures, the applicant proposes to follow women exposed to ustekinumab during pregnancy under a registry established in Scandanavia (Sweden, Denmark) for infliximab. It is described as “a prospective, 5-year observational study of pregnancy outcomes in pregnant women with prenatal exposure to (product) in actual clinical practice, and of health status of their infants who have had prenatal exposure to (product) during a one-year follow-up period. This will be a current exposure-based cohort study in which women with diseases of interest but without prenatal (product) exposure, and their infants, will serve as controls.” Treatments are as prescribed by the physician on the basis of usual clinical practice. The exposure interval of interest is from 3 months prior to conception through birth. The duration of study participation for maternal patients is from the first prenatal care visit through post-delivery hospital discharge and for infant patients from birth to age 12 months. The sources of data are several Swedish and Danish national health registries:

**Comment:** The review division consulted the Maternal Health Team (MHT) regarding the adequacy of the applicant’s proposed plans for post-marketing assessment of pregnancy exposures/outcomes. From the consult provided by Leyla Shahin, M.D:

Regarding the proposed Scandinavian pregnancy registry, Dr. Shahin concluded that “Use of these databases alone for outcomes data on pregnancies exposed to Ustekinumab has a number of significant limitations. The Swedish Medical Birth Register contains information on pregnancy outcomes on all live births, and only on fetal deaths after 28 weeks gestation. It is not clear what outcomes are available in the Danish Medical Birth Register. While the Scandinavian

Clinical Review  
Brenda Carr, M.D.  
BLA 125261  
Ustekinumab

*pregnancy registry is valuable because of its ability to use established databases, it would not capture important information about pregnancy losses up to 28 weeks gestation. The United States has a more heterogeneous and significantly larger population than the Scandinavian countries, and it is not clear that data findings from Sweden and Denmark could be accurately generalized to the U.S. population.”*

*The North American Adverse Event Registry (PSOLAR) was determined to be an inadequate surveillance tool for evaluation of pregnant women exposed to ustekinumab, “although a prospective study, (it) does not include details regarding surveillance of adverse events in pregnancy, collection of data regarding terminations, and follow-up of neonates after birth. It also doesn't mention a control group of pregnant women.”*

*The MHT recommended that the applicant establish a pregnancy registry based in the United States (i.e. in addition to the proposed Scandinavian registry).*

*Ustekinumab is excreted in the milk of lactating monkeys. The MHT is therefore also recommending a lactation study.*

### 7.6.3 Pediatrics and Effect on Growth

Pediatric use has not been evaluated. At the EOP2 meeting, the Agency agreed to the applicant's request for a deferral of pediatric studies. The applicant sites two reasons for the requested deferral in the BLA:

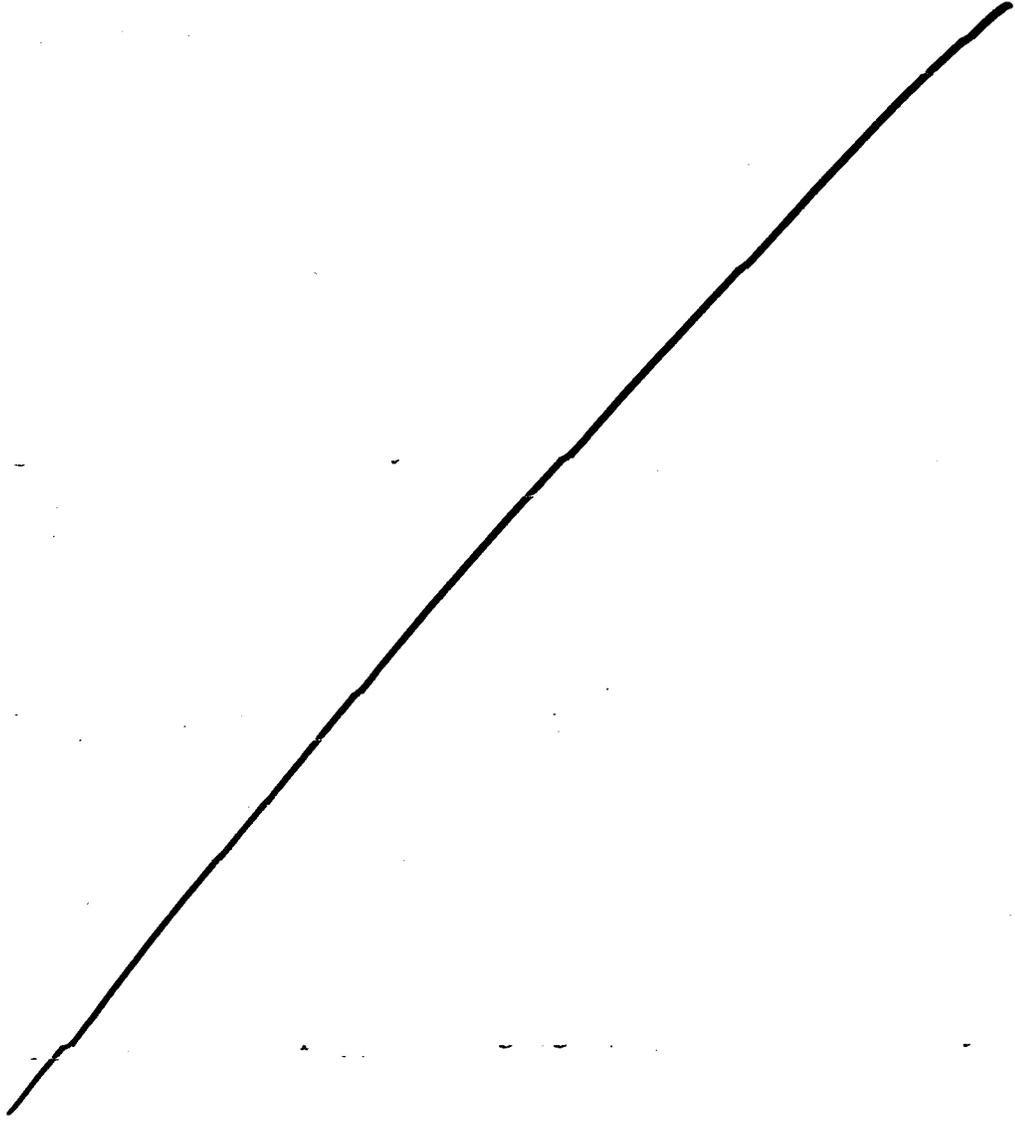
- a small unmet medical need
- a desire to “gain additional safety experience in the adult population prior to exposing a pediatric population to a first-in class systemic biologic.”

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

b(4)



b(4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The reviewer is not aware of any overdose experience with the product, and considers the potential for abuse to be limited. Rebound has been previously discussed.

## 7.7 Additional Submissions

This section of the review will discuss:

- the submission of proposed proprietary name
- the Safety Update (submitted on April 4, 2008)
- the Malignancy Position Paper and Enhanced Risk Management Plan (July 17, 2008)
- the applicant's response to Information Request (August 15, 2008)

### PROPOSED PROPRIETARY NAME

The applicant proposes the proprietary name Stelara for ustekinumab. The name was submitted for review on May 23, 2007 under IND 9590 (Serial 202). Per the cover letter to the marketing application, the name has been accepted by the CHMP Invented Name Review Group of the European Agency for the Evaluation of Medicinal Products (EMA).

In the consult with signature dates March 7 and 10, 2008, the Division of Medication Errors and Technical Support (DMETS) found the proposed name Stelara unacceptable because of its orthographic similarity to Stalevo, a product marketed in the United States for treatment of idiopathic Parkinson's disease:

"Stalevo is orthographically similar to Stelara because the first four letters of the names ('STAL' vs. 'STEL') and the last three letters of the names ('evo' vs. 'ara') look similar when scripted." (See below from the DMETS consult.)

Stalevo                      Stelara

On April 18, 2008, the applicant submitted a request for reconsideration of Stelara as the proposed tradename for ustekinumab. In support of this request, the applicant submitted two reports from studies conducted by the \_\_\_\_\_ at the request of the applicant. One study ("Regulatory / Safety Analysis for the Proposed Proprietary Name Stelara") was undertaken to assess the risk of medication errors between Stelara and other marketed drug names in the United States and Europe. The other study ("Failure Mode & Effects Analysis (FMEA) - STELARA™") was undertaken to "prospectively identify, analyze and propose mitigation strategies for potential failure modes or medication errors that may arise due to the co-existence of Stelara and Stalevo in the US marketplace." The applicant believes that the studies provide evidence that there is "minimal potential" for confusion (verbal, print or handwritten) between Stelara and Stalevo.

b(4)

*Comment:* The applicant describes the \_\_\_\_\_ as "a leading independent consultancy in the area of pharmaceutical brand name development." The applicant's request for reconsideration of the proposed proprietary name Stelara and the \_\_\_\_\_ reports were forwarded to DMETS for review, and their final opinion was pending as the clinical review was closing.

b(4)

**SAFETY UPDATE**

The Safety Update was submitted on April 4, 2008. It provided for an additional 6 months of safety data from the ongoing Phase 3 studies, T08 and T09 and from the Phase 2 study in psoriatic arthritis, C0743T10. The update also provided for preliminary safety results (through week 12) from the Phase 3 active-controlled study in which ustekinumab is being compared to etanercept, C0743T12 (also known as ACCEPT). No new safety concerns were raised by the information submitted in the Safety Update.

**Phase 3 Studies (T08 and T09)**

The Safety Update provided an additional 6 months of safety data, making for extent of exposures as in the table below:

**Duration of exposure through 18 months (Source: Safety Update Table 2)**

	45 mg N= 1110	90 mg n= 1156
Duration of ustekinumab exposure		
At least 6 months <sup>a</sup>	994 (89.5%)	976 (84.4%)
At least 1 year <sup>b</sup>	645 (58.1%)	640 (55.4%)
At least 18 months <sup>c</sup>	187 (16.8%)	186 (16.1%)
Avg number of injections administrations	5.0	4.7
Mean dose ± SD	224.1 ± 81.38	422.1 ± 169.63
Range	(45, 405)	(45, 900)

<sup>a</sup> The duration between the first and last CNTO 1275 administration was at least 14 weeks.

<sup>b</sup> The duration between the first and last CNTO 1275 administration was at least 38 weeks.

<sup>c</sup> The duration between the first and last CNTO 1275 administration was at least 62 weeks.

**Serious Adverse Events**

One additional report of death was included, and this subject (09-019-042) was discussed in Section 7.3.1 of this review. As was the case with the data reported in the ISS, serious adverse events were most frequently reported in the cardiac disorders (4 subjects) and infections and infestations (7 subjects) system-organ classes.

Of the subjects with serious adverse events in the cardiac disorders system-organ class 3 were in the 45 mg group, and 1 was in the 90 mg group:

- 45 mg: MI (41 y/o M; hyperlipidemia; 3 vessel disease); coronary artery disease (43 y/o M; smoker and family hx of CAD; underwent stent placement); coronary artery disease (53 y/o M; 5-vessel disease ; underwent 5-vessel CABG)
- 90 mg: chest pain (52 M; hx of HTN, CHF, coronary artery disease CVA, HTN, TIA, hyperlipidemia, HTN; underwent CABG with 8 grafts)

Of the 7 new subjects with serious adverse events in the infections and infestations system-organ class, 5 were in the 45 mg group, and 2 were in the 90 mg group:

- 45 mg: diverticulitis (49 y/o F; history of same); erysipelas (43 y/o M; associated with superficial wound on leg); cellulitis (68 y/o M; on left foot; diagnosed 9 days after surgery on same foot), cholecystitis (40 y/o M; obese; had cholecystectomy), and, facial palsy (43 y/o M; CVA ruled out; Bell's palsy diagnosed)
- 90 mg groups: pneumonia (52 y/o F; hemoptysis no acute changes on CXR; no AFB; few Gm – rods and Gm + cocci; final diagnosis “atypical pneumonia”) and genitourinary

tract infection (38 y/o M; had fever & malaise; no hematuria; no information re cultures or prostate)

### Malignancies

There were 7 additional subjects reported with malignancies through the database lock periods for the Safety Update (database lock was Week 76 for T08 and Week 52 for T09). Four subjects had NMSC. Regarding the other 3 subjects:

1. Subject 105-007: colon cancer

This subject was a 62 y/o F who was randomized to the 45 mg group. She reportedly had "repeat" low hemoglobin values and occult blood in stool samples. She was diagnosed with microcytic anemia on May 22, 2007. She had a colonoscopy the same day which revealed a lesion encircling the lumen, and colon cancer was diagnosed on May 25, 2007. She underwent right hemicolectomy. The pathology report described a moderately differentiated adenocarcinoma invading the serosal fat arising from a tubulovillous adenoma, and several regional lymph nodes were involved with tumor.

2. Subject 010-016: tongue neoplasm, malignant

This subject was a 70 y/o M who was randomized to the 90 mg group. He was said to have had a "canker sore" on the back of his tongue from September 2 to November 15, 2006. On January 15, 2007, he noticed a lesion on the back of his tongue. Biopsy of a posterior tongue (the narrative does not specify this as being the same lesion the subject had noted) showed a well-differentiated invasive squamous cell carcinoma with no evidence of lymphovascular space invasion. He underwent resection.

3. Subject 014-017: malignant melanoma in situ

This subject was a 54 y/o M who was randomized to the 90 mg group. He was reported to have noticed a mole behind his left ear on May 23, 2007. Biopsy done on May 31, 2007, and the results reported as malignant melanoma in situ.

**Comment:** *An additional 3 serious malignancies were reported outside of the database lock, all were reported from study T09. It is noted that no additional serious malignancies were reported from study T08, the study with the Week 76 datalock:*

- *Subject 010-001: This subject was a 59 y/o male (90mg) who was diagnosed with prostate cancer. He had had an elevated PSA for an unspecified period. Histology was not provided, but 1 to 2% of the left lobe was said to be affected. He underwent radical prostatectomy on \_\_\_\_\_*
- *Subject 118-010: This was a 55 y/o F (90 mg) who was diagnosed with endometrial cancer. She had experienced spotting and underwent endometrial biopsy on August 10, 2007, and was diagnosed with endometrial carcinoma. She was admitted on \_\_\_\_\_ and had a total abdominal hysterectomy and bilateral salpingoophorectomy with a pelvic and para-aortic lymphadenectomy (pathology: noninvasive adenocarcinoma of the endometrium, Grade 2).*
- *Subject 404-019: This was a 63 y/o M (45 mg) who was diagnosed with adenocarcinoma of the pancreas on November 26, 2007. Biopsy results showed adenocarcinoma of the head of the pancreas. He reportedly had "long-standing"*

b(6)

*history of abdominal pain. He was reported to have had serious adverse events of abdominal pain in November 2006 and June 2007.*

The following table (Table 6 from the Safety Update) presents an analysis of malignancies (it does not include the 3 malignancies that occurred outside of datalock):

**Number of subjects with 1 or more malignancies through the end of the reporting period; treated subjects in psoriasis Phase 2 and Phase 3**

	Placebo	45 mg	90 mg	Combined
Subjects treated <sup>a</sup>	732	1110	1156	2266
<b>Type of malignancy</b>				
<b>Nonmelanoma skin cancer</b>				
Total subject-years of follow-up	182	1111	1134	2245
Median subject-years of follow-up	0.2	1.0	1.0	1.0
Observed number of subjects	2	7	11	18
Incidence per 100 subject-years	1.10	0.63	0.97	0.80
95% confidence interval <sup>b</sup>	(0.13, 3.98)	(0.25, 1.30)	(0.48, 1.74)	(0.48, 1.27)
<b>Malignancies other than nonmelanoma skin cancer</b>				
Total subject-years of follow-up	182	1111	1138	2249
Median subject-years of follow-up	0.2	1.0	1.0	1.0
Observed number of subjects	1	7	1	8
Incidence per 100 subject-years	0.55	0.63	0.09	0.36
95% confidence interval <sup>b</sup>	(0.01, 3.06)	(0.25, 1.30)	(0.00, 0.49)	(0.15, 0.70)
<b>All malignancies</b>				
Total subject-years of follow-up	181	1108	1134	2242
Median subject-years of follow-up	0.2	1.0	1.0	1.0
Observed number of subjects	3	14	12	26
Incidence per 100 subject-years	1.65	1.26	1.06	1.16
95% confidence interval <sup>b</sup>	(0.34, 4.83)	(0.69, 2.12)	(0.55, 1.85)	(0.76, 1.70)

<sup>a</sup> Placebo crossover subjects were included in CNTO 1275 columns after crossover to CNTO 1275.

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

*Comment: The provided data raise no new concerns regarding the malignancy risk.*

### **C0743T10**

Database lock was at Week 36 for this Phase 2 study in which ustekinumab is being evaluated for treatment of psoriatic arthritis. This study is now complete. The Safety Update provides safety data for 133 subjects treated with ustekinumab.

Subjects were followed through Week 36. There are two dosing groups:

- Group 1: 90 (or 63) mg of ustekinumab SC at Weeks 0, 1, 2, 3 and placebo at Weeks 12 and 16
- Group 2: 90 (or) 63 mg of placebo SC at Weeks 0, 1, 2, 3 and ustekinumab at Weeks 12 and 16.

There were no deaths in the study. During the first 12 weeks, 3 serious adverse events were reported, and all occurred in the placebo group (see Section 7.4.1). Six additional serious adverse events were reported in the update:

- Subject 002-018: This 63 y/o F was admitted for an event of chest pain. She had a history of HTN, CVA, CAD (with angioplasty and stent placement). She was discharged with a diagnosis of angina.
- Subject 003-011: This was a 57 y/o F with an event of syncope, and cause was not determined.
- Subject 016-004: This was a 48 y/o F who had a hemorrhagic stroke. She presented with a "severe unrelenting" headache and progressive decline in neurologic status. She was hospitalized with a diagnosis of left cerebral vascular accident with intracranial hemorrhage, though likely due to a vertebral artery dissection. The final diagnosis was reported as left vertebral artery dissection with hemorrhagic stroke. ["Left middle cerebral artery (MCA) aneurysm for which they are considering coil embolization"].
- Subject 102-002: This was a 56 y/o M who experienced the adverse events of HTN, MI and CHF. His past medical history included CHF, angina, viral cardiomyopathy, Type 2 DM, and smoking. He experienced exertional SOB, chest pain and diaphoresis. He was diagnosed with HTN, CHF and MI (although no evidence on ECG and "limited" enzymatic evidence). Cardiac catheterization revealed long standing, inoperable coronary artery disease.
- Subject 102-006: This 40 y/o F had an event of "pelvic mass." She never received ustekinumab. She underwent a diagnostic laparoscopy and pelvic laparotomy with lysis of adhesions and excision of right adnexal mass. Postoperative diagnosis was extensive pelvic adhesions, right endometrioma, and hemorrhagic cyst right adnexa.
- Subject 301-007: This 26 y/o F had an adverse event of "respiratory tract infection." She complained of runny nose, cough, sore throat, fever (39°C), and shortness of breath. She was admitted to the hospital with a respiratory tract infection. The discharge diagnosis was acute bronchitis.

There were no opportunistic infections. There was one malignancy reported: basal cell carcinoma.

### **C0743T12: A Phase 3, Multicenter, Randomized Study Comparing CNTO 1275 and Etanercept for the Treatment of Moderate to Severe Plaque Psoriasis (ACCEPT)**

Primary objective: To compare the efficacy of ustekinumab to etanercept and evaluate the safety

of ustekinumab and etanercept in the treatment of subjects with moderate to severe plaque psoriasis.

**Trial Design:** This is a multicenter, randomized study of 2 dosing regimens of ustekinumab or a 50 mg twice weekly dosing regimen of etanercept in subjects with moderate to severe psoriasis, who had an inadequate response to, were intolerant to, or had a contraindication to cyclosporine, methotrexate (MTX) or psoralen plus ultraviolet A light (PUVA).

**Comment:** *This is evaluating both products as second-line therapies.*

**Treatment arms/Dose regimens through Week 12:** Approximately 850 subjects were to be randomized in a 3:5:5 ratio to 1 of 3 treatment groups as follows:

- Group 1: Ustekinumab 45 mg at Weeks 0 and 4
- Group 2: Ustekinumab 90 mg at Weeks 0 and 4
- Group 3: Etanercept 50 mg twice weekly through Week 12.

**Comment:** *The regulatory intent of this study is unclear. The applicant has been advised that it would not provide adequate evidence to support any labeling claims, as 2 studies would be necessary. Additionally, the study compared the safety and efficacy only of the loading regimens and provides no information on how the products compare with longer term dosing, as would be the use in clinical practice. The population evaluated is somewhat different than population studied in Phase 3 and proposed as the target population in the marketplace.*

**Method of Treatment Assignment:** Eligible subjects were randomized at Week 0. Randomization was stratified by investigational site and baseline weight (< 90 kg or ≥90 kg).

**Treatment duration/Trial duration:** 12 weeks for initial treatment/64 weeks.

**Primary endpoint:** The proportion of subjects who achieve ≥75% improvement in PASI from baseline (PASI 75 responders) at Week 12.

**Distribution of Study Subjects:** A total of 903 subjects were randomized:

- 209 to ustekinumab 45 mg,
- 347 to ustekinumab 90 mg and
- 347 to etanercept.

#### **Deaths and Other Serious Adverse Events**

There were no deaths through Week 12.

The rates of serious adverse events were comparable between treatment groups, and no event was reported in more than one subject. Serious infections were reported for

- 1 (0.3%) etanercept subject (bacterial meningitis), and
- 4 (0.7%) ustekinumab subjects (all receiving 90 mg; 1 subject each had an uncomplicated appendicitis, a gastrointestinal infection secondary to food poisoning, uvulitis, and 1 subject had both urosepsis and a nosocomial staphylococcal pneumonia).

**Appendix D.7 Number of subjects with 1 or more treatment-emergent serious adverse events through Week 12 by MedDRA system-organ class and preferred term; treated subjects**

	Etanercept	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated	347	209	347	556
Avg duration of follow-up (weeks)	12.1	12.1	12.2	12.2
Avg exposure (number of administrations)	23.1	2.0	2.0	2.0
Subjects with 1 or more serious adverse events	4 (1.2%)	4 (1.9%)	4 (1.2%)	8 (1.4%)
<b>System-organ class/preferred term</b>				
Gastrointestinal disorders	1 (0.3%)	1 (0.5%)	2 (0.6%)	3 (0.5%)
Gastritis	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Pancreatitis	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Peptic ulcer haemorrhage	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Uvulitis	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Abdominal pain upper	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections and infestations	1 (0.3%)	0 (0.0%)	3 (0.9%)	3 (0.5%)
Appendicitis	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Gastrointestinal infection	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Pneumonia staphylococcal	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Urosepsis	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Meningitis bacterial	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Myocardial infarction	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
General disorders and administration site conditions	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Chest pain	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Breast cancer	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Psychiatric disorders	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Psychotic disorder	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Renal and urinary disorders	1 (0.3%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Renal failure acute	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)
Nephrolithiasis	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Hypertension	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rotator cuff syndrome	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Adverse events that occurred in  $\geq 5\%$  of subjects are presented in the following table:

**Table D.3 Number of subjects with 1 or more treatment-emergent adverse events (with frequency of 5% or greater in any treatment group) through Week 12 by MedDRA preferred term; treated subjects**

	Etanercept	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated	347	209	347	556
Avg duration of follow-up (weeks)	12.1	12.1	12.2	12.2
Avg exposure (weeks)	23.1	2.0	2.0	2.0
Subjects with 1 or more adverse events	241 (69.5%)	138 (66.0%)	237 (68.3%)	375 (67.4%)
<b>Preferred terms</b>				
Headache	38 (11.0%)	31 (14.8%)	41 (11.8%)	72 (12.9%)
Nasopharyngitis	29 (8.4%)	21 (10.0%)	34 (9.8%)	55 (9.9%)
Upper respiratory tract infection	20 (5.8%)	13 (6.2%)	22 (6.3%)	35 (6.3%)
Back pain	7 (2.0%)	14 (6.7%)	15 (4.3%)	29 (5.2%)
Pruritus	14 (4.0%)	12 (5.7%)	16 (4.6%)	28 (5.0%)
Fatigue	13 (3.7%)	8 (3.8%)	19 (5.5%)	27 (4.9%)
Arthralgia	9 (2.6%)	11 (5.3%)	10 (2.9%)	21 (3.8%)
Injection site erythema	51 (14.7%)	2 (1.0%)	2 (0.6%)	4 (0.7%)
Injection site swelling	25 (7.2%)	3 (1.4%)	0 (0.0%)	3 (0.5%)

Generally, the most common adverse events overall were headache and nasopharyngitis. This differs somewhat from the patterns seen in the psoriasis studies combined for analyses in the ISS, where nasopharyngitis and upper respiratory tract infection were the most common events. Injection site reactions were far more frequently reported in the etanercept than in ustekinumab groups (even if the groups were combined). No cases of tuberculosis or serious opportunistic infections were observed.

One myocardial infarction was reported (ustekinumab 90 mg group). Past medical history for this subject included hypertension, diabetes with advanced diabetic neuropathy, peripheral arterial disease, a below the knee amputation, hyperlipidemia and coronary artery disease. In addition, the event occurred in the setting of urosepsis, acute renal failure and upper GI bleed requiring transfusion.

Malignancies were reported in 4 subjects, all of whom received ustekinumab:

- 1 subject with basal cell carcinoma (90 mg)
- 1 subject with squamous cell carcinoma (45 mg)
- 1 subject with basal and squamous cell carcinoma (45 mg)
- 1 subject with breast cancer (45 mg)

The skin cancers were noted in areas where psoriasis had cleared with treatment. The breast cancer occurred in a 58 y/o F who had a family history of same (mother). She was randomized

Clinical Review  
 Brenda Carr, M.D.  
 BLA 125261  
 Ustekinumab

on May 23, 2007 (45 mg) and a mammogram done July 11, 2007 revealed architectural changes not present on a December 2006 study. She was diagnosed with invasive lobular carcinoma and had a separate focus of invasive well-differentiated ductal carcinoma. One of 17 nodes was positive for lobular histology.

*Comment: The reviewer does not consider it likely that ustekinumab could have been causative, given that she was diagnosed with metastatic disease within approximately 7 weeks of randomization.*

A summary of safety information from the ACCEPT study is presented in the following table:

**Table D.2 Summary of key safety information through Week 12; treated subjects\**

	Etanercept	Ustekinumab		
		45 mg	90 mg	Combined
Subjects treated	347	209	347	556
Avg duration of follow-up (weeks)	12.1	12.1	12.2	12.2
Avg exposure (number of administrations)	23.1	2.0	2.0	2.0
Subjects with AEs leading to discontinuation of study agent	8 (2.3%)	4 (1.9 %)	4 (1.2%)	8 (1.4%)
Subjects with 1 or more:				
Adverse events	241 (69.5%)	138 (66.0%)	237 (68.3%)	375 (67.4%)
Injection site reactions	77 (22.2%)	6 (2.9%)	7 (2.0%)	13 (2.3%)
Serious adverse events	4 (1.2%)	4 (1.9%)	4 (1.2%)	8 (1.4%)
Infections	93 (26.8%)	59 (28.2%)	93 (26.8%)	152 (27.3%)
Infections requiring treatment	34 (9.8%)	18 (8.6%)	31 (8.9%)	49 (8.8%)
Serious infections	1 (0.3%)	0 (0.0%)	4 (1.2%)	4 (0.7%)
Malignant neoplasms	0 (0.0%)	3 (1.4%)	1 (0.3%)	4 (0.7%)
NMSC <sup>a</sup>	0 (0.0%)	2 (1.0%)	1 (0.3%)	3 (0.5%)
Malignancy other than NMSC <sup>a</sup>	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.2%)
Major adverse cardiovascular events <sup>b</sup>	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.2%)

<sup>a</sup>NMSC = non-melanoma skin cancers

<sup>b</sup>Major adverse cardiovascular event, including cardiovascular death, myocardial infarction, or stroke.

*Comment: No new safety concerns were raised. Some imbalance in numbers of ustekinumab subjects compared to etanercept, as more subjects randomized to former (because of 2 dosing groups, 45 mg and 90 mg).*

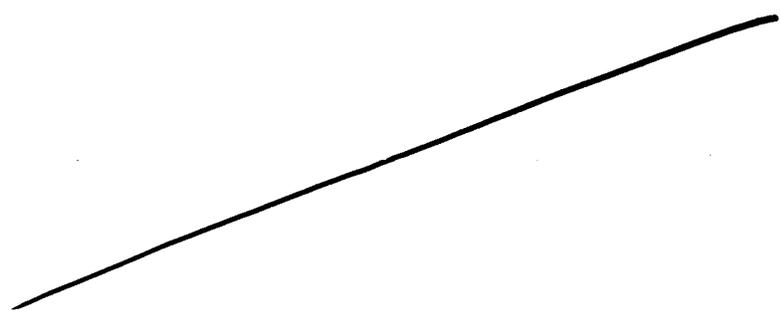
## **MALIGNANCY POSITION PAPER and ENHANCED RISK MANAGEMENT PLAN**

These items were submitted July 17, 2008 in follow-up to the Advisory Committee meeting held June 17, 2008. The submission constituted a major amendment. Some summary points from each of these documents are presented below.

### **Malignancy Position Paper**

In crafting the Malignancy Position Paper, the applicant referenced the original submission and publically available information on other biologics approved for treatment of psoriasis, e.g. approved product labeling, Advisory Committee transcripts. The applicant believes that the clinical database provides substantial information about the potential impact of ustekinumab on malignancy. They acknowledged the theoretical risk of malignancy and noted their proposal to include relevant information regarding malignancy in the Warnings/Precautions section in the ustekinumab label.

*Comment: 1) The Advisory Committee did not believe the database to be sufficient in size or duration of follow-up to address low frequency or long latency events. The reviewer agrees with the Advisory Committee.*



b(4)

The applicant believes that the level of concern about malignancy does not warrant a mandatory registry or "other post-marketing burdens." They believe that an Enhanced Risk Management Plan is a "more appropriate, comprehensive, and scientifically sound plan for post-marketing assessment of any malignancy risk of ustekinumab."

*Comment: 1) While no formal vote was taken, most members of the Advisory Committee were in favor of a mandatory registry. The reviewer agrees with the applicant and does not recommend a mandatory registry for purposes of assessment of a theoretical risk (as opposed to management of a known serious risk). No signal emerged in the safety database to merit a mandatory registry. However, the reviewer does recommend that a REMS be required for this product. It is unclear what the applicant would consider to be "other post-marketing burdens," since some sort of comprehensive pharmacovigilance and risk minimization strategy would be appropriate and*

*required for this first-in-class product (the use of which might theoretically pose specific infectious risks and malignancy risk).*

Per the applicant, the extent to which the animal findings suggesting a malignancy risk from IL-12/23 blockade can be extrapolated to humans is unclear. The applicant states that the nonclinical toxicology package for ustekinumab, which includes data in nonhuman primates, did not suggest a malignancy risk [based on measures of immune function (peripheral and functional) and necropsy data]. The applicant cites in contrast certain findings from primate toxicology studies conducted in the development programs for other systemic biologics approved for treatment of psoriasis. The specific examples cited were:

- Amevive (alefacept): B-cell lymphoma in one monkey after 28 weeks of dosing; B-cell hyperplasia of the spleen and lymph nodes in other animals; alefacept-treated baboons showed “centroblast proliferation in B-cell dependent areas in the germinal centers of the spleen”
- Raptiva (efalizumab): reticular cell hyperplasia in paracortical areas of biopsied lymph node in chimpanzees

**Comment:** *The reviewer agrees with the applicant that it is not clear that the findings in animals will apply to humans. The data from the applicant’s 6-month monkey study were not adequate to rely on for definitive conclusions regarding malignancy risk of ustekinumab because the study “did not provide treatment durations that cover(ed) a sufficiently long duration of the monkey life span” (see Section 4.3). The reviewer acknowledges that a malignancy signal was seen in a primate study pre-approval in the development program for at least one biologic currently marketed for treatment of psoriasis, and no mandatory registry was required.*

Per the position paper, there are IL-12 independent pathways for production of IFN $\gamma$ , an important cytokine in anti-tumor responses in rodents through which the anti-tumor effects of IL-12 are mediated. In contrast, per the applicant, IL-23 blocks IFN $\gamma$  in rodent models. Blockade of IL-12/23 may have opposing effects, since there are reports (mouse models) that IL-23 may promote tumor incidence and growth. The applicant also presents information suggesting that the biology of IL-12/23 in rodents may differ from that in humans, e.g. exogenous IL-12 was not proven to be safe or effective for treatment of cancer in humans.

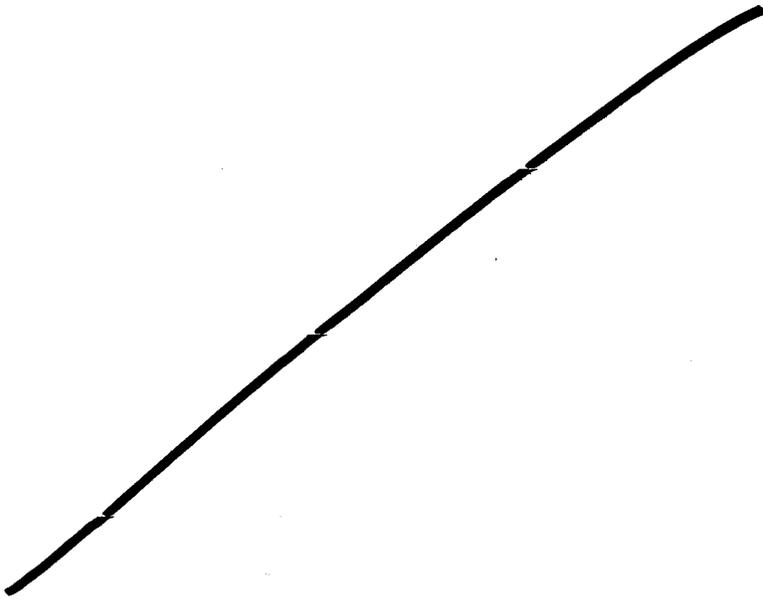
**Comment:** *The applicant presents a persuasive case that in animal models IFN $\gamma$  production may not be totally suppressed by blockade of IL-12, and that it is possible that the malignancy risk that might attach to IL-12 blockade may in certain settings be offset by the simultaneous blockade of IL-23. The reviewer agrees with the applicant that it is unclear how the findings in animal models might translate to humans; however, it is precisely this uncertainty robust post-approval assessment imperative.*

There are 5 biologics approved for treatment of psoriasis: alefacept, efalizumab, etanercept, infliximab, and adalimumab. Alefacept is a leukocyte function-associated antigen (LFA)-3-immunoglobulin fusion protein. Efalizumab is an anti-CD11a monoclonal antibody. Etanercept, infliximab, and adalimumab are TNF $\alpha$  blockers. Per the applicant, “all of these mediators (or the cells that bear them) are believed to play a role in immune surveillance against neoplasia” (in animal models).

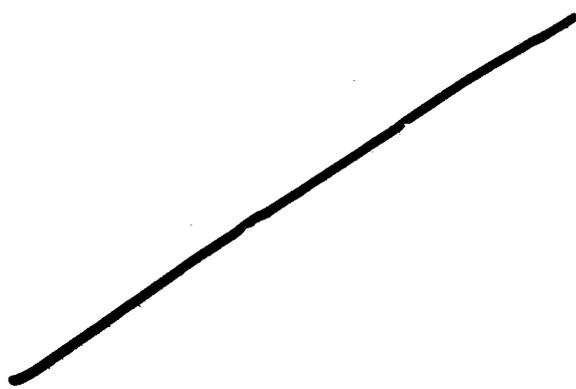
The applicant also discusses the clinical experience with humans who are genetically deficient in functional IL-12/23:

- There have been no reports of malignancy in these patients (although the applicant states a case of esophageal carcinoma was verbally communicated to them). However, the applicant also notes that “most patients in the reported case series are in childhood or early adulthood.”
- Their susceptibility to pathogens appears to be more limited than animal models might have predicted: disseminated BCG, environmental mycobacteria and non-typhoidal salmonella.
- There are genetically-affected siblings who “are” phenotypically normal.

*Comment: This information is generally consistent with what the reviewer has read about the genetic deficient state(s).*



b(4)



b(4)

**RESPONSE to INFORMATION REQUEST**

On August 15, 2008, the Agency forwarded an Information Request which, in part, requested information on the Nordic Database Initiative, and the pharmacovigilance activities modeled after the FDA's Sentinel Initiative and PSOLAR.

**Nordic Database Initiative**

The Nordic Database Initiative (NDI) is a proposed prospective, 5+year extendable study of adverse events in all psoriasis patients in Sweden treated with ustekinumab in actual clinical practice. Per the applicant, Sweden has several healthcare databases that together capture information on all persons living in Sweden. The applicant intends to combine the data from these registers into one analytical data set, and the applicant states this will capture all psoriasis patients in Sweden and provide the denominator for comparison of adverse events of interest. Per the applicant, the data set would allow for several comparisons, including by disease and indication and with or without ustekinumab exposure. They ultimately expect to follow approximately 4,000 ustekinumab patients for at least 10 years; however, the number of patients in the data set will be a function of both the number of moderate to severe psoriasis patients in Sweden and the uptake of ustekinumab.

*Comment: From the description in Table 23 of the Risk Management Program, it appears that this was initially intended to capture postmarketing safety information on pregnancies. The applicant should submit a complete protocol for this proposed study.*

---

b(4)

### **Pharmacovigilance Activities Modeled after the FDA's Sentinel Initiative**

The operational plan for these activities would entail:

- identifying the managed care databases with the most ustekinumab uptake.
- developing protocols to evaluate the incidence of malignancies or serious infections in identified databases.
- conducting studies and submitting results to the Agency.
- educating physicians and patients on study outcomes (should results warrant this).

## **8 Postmarketing Experience**

The product is not marketed anywhere. However, in the original submission, the applicant proposed the following risk management plan (subsequently "enhanced" as described above):

The remainder of this page is left intentionally blank.

Source: Applicant's Risk Management Plan

**Table 25 Overview of study protocols for the pharmacovigilance plan**

Study	Protocol Version	Study Status	Planned/Estimated Date for Submission of Interim Data	Planned/Estimated Date for Submission of Final Data
Long-term extension Phase 3 PSO study C0743T08	26 Jan 2007	Ongoing	Mar 2008	Dec 2011
Long-term extension Phase 3 PSO study C0743T09	26 Jan 2007	Ongoing	Mar 2008	May 2012
Etanercept comparator study C0743T12	22 Aug 2007	Ongoing	Oct 2008	Oct 2009
PSOLAR (Psoriasis registry)	07 Aug 2007	Ongoing*	1 year post-approval	To be determined
Pregnancy Research Initiative	19 Jun 2006	Ongoing*	1 year post-approval	To be determined
Nordic Database Initiative	NA (protocol not finalized)	Planned	TBD	TBD

TBD – to be determined

\*Ongoing for infliximab and other therapies

1. Long-term extension of the Phase 3 psoriasis trials

The safety and efficacy of long-term continuous use of ustekinumab will be evaluated through 5 years from initial administration of product (264 weeks). The extension period begins at Week 52 in both studies, and subjects will continue the same dose and frequency of treatment as they were receiving at that time point. Study C0743T08 will remain blinded until all subjects have completed Week 76 and study C0743T09 until all subjects have completed Week 52. The databases will be locked at these respective time points. After, unblinding of the studies, dose intervals may be adjusted or dose escalation is allowed at the investigator's discretion.

2. Etanercept comparator study (study C0743T12)

This ongoing Phase 3 study is evaluating ustekinumab 45 mg and 90 mg, and etanercept 50 mg in approximately 850 subjects with moderate to severe plaque psoriasis. The active-controlled portion of the study is from Week 0 to Week 12 during which the efficacy and safety of etanercept and 2 dose levels of ustekinumab will be evaluated. Treatment after Week 12 is dependent on Physician's Global Assessment (PGA) response at Week 12 and initial treatment assignment. Subjects will have scheduled follow-up visits at Weeks 2, 4, and every 4 weeks thereafter through Week 64. The end of the study is defined as the time the last subject completes the Week 64 visit.

3. PSoriasis Longitudinal Assessment and Registry

The PSoriasis Longitudinal Assessment and Registry (PSOLAR; study C0168Z03) is ongoing for infliximab, and patients treated with ustekinumab should be added when appropriate. It is based in North America and designed to collect data on psoriasis patients eligible to receive systemic therapies, including generalized phototherapy and biologics. It is intended to track adverse events in approximately 8,000 patients, and the applicant projects that 4,000 of these patients will have been exposed to ustekinumab.

The registry will actively collect all serious adverse events and other targeted adverse events (malignancies, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, congestive heart failure, hepatotoxicity, and hematologic events). The registry will also collect data on disease activity and on pregnancy outcomes. The applicant anticipates that the registry will last 8 years from the enrollment of the last subject.

#### 4. Pregnancy Research Initiative (study C0168T71)

This initiative is ongoing for infliximab and patients treated with ustekinumab exposure should be added when appropriate. It is a prospective, 5-year observational study of pregnancy outcomes in pregnant women with prenatal exposure to in actual clinical practice, and of health status of their infants who have had prenatal exposure to ustekinumab during a one-year follow-up period. This will be a current exposure-based cohort study in which women with diseases of interest but without prenatal ustekinumab exposure, and their infants, will serve as controls.

#### 5. Nordic Database Initiative

The applicant proposes to utilize the northern European national medical and pharmaceutical data sets (whole population) to collect post-marketing safety information on pregnancy. The applicant believes these data sets offer the ability to monitor adverse event information over a large geographic region, along with other covariables such as medication history and clinical outcomes. By utilizing multiple Northern European registries simultaneously, the applicant believes it possible to perform surveillance on populations that may exceed 20 million in size.

These large databases can potentially capture more rare adverse events than might be captured in targeted (e.g. disease-specific registry) initiatives. Furthermore, they offer the ability to perform analyses free of several sources of enrollment bias. The applicant will query these data sets for adverse events of special interest, such as malignancies, infections, cardiovascular events, and deaths over the entire national populations that can include Sweden and other northern European countries. These analyses will be compared/contrasted where relevant with outcomes from a disease/agent-specific registry based in North America.

The applicant proposed the following risk minimization plans:

1. Product labeling which would provide guidance about serious infections and malignancy
2. An educational program to provide tools to help optimize the benefit-risk profile; objectives would include
  - education of physicians on selection of appropriate patients
  - education of physicians and patients on potential serious side effects

*Comment: The applicant should submit a REMS, to consist of a Medication Guide and a Communiation Plan..*

## 9 Appendices

### 9.1 Literature Review/References

1. Torti DC, Feldman SR. Interleukin-12, interleukin-23 and psoriasis: Current prospects. *J Am Acad Dermatol* 2007;57:1059-68.
2. Mehlis SL, Gordon KC. The immunology of psoriasis and biologic immunotherapy. *J Am Acad Dermatol* 2003;49:S44-50.
3. Stern RS, Lunder EJ. Risk of squamous cell carcinoma and methoxsalen (psoralen) and UV-A radiation (PUVA). *Arch Dermatol*.1998;134:1582-1585.
4. Ozbek N, Fieschi C, Yilmaz B, de Beaucoudrey L, Demirhan B, Feinburg J, et al. Interleukin-12 receptor  $\beta$ 1 chain deficiency in a child with disseminated tuberculosis. *Clinical Infectious Diseases* 2005;40:e55-8.
5. Kumararatne D. Mendelian susceptibility to mycobacterial disease. *Respiration* 2006;73:280-282.
6. Sanal O, Turul T, De Boef T, Van De Vosse E, Yalcin I, Tezcab I. Presentation of interleukin-12/-23 receptor  $\beta$ 1 deficiency with various clinical symptoms of salmonella infections. *Journal of Clinical Immunology*, Vol. 26, No. 1, January 2006.
7. Picard C, Fieschi C, Altare F, Al-Jumaah S, Al-Hajjar S, Feinberg J et al. Inherited interleukin-12 deficiency; *IL12 $\beta$*  genotype and clinical phenotype of 13 patients from six kindreds. *Am J Hum Gen* 70:336-348,2002.
8. Casanova JL. Mendelian susceptibility to mycobacterial infection in man. *Swiss Med Wkly* 2001;131:445-454.
9. Altare F, Lammas D, Revy P, Jouanguy E, Doffinger R, Lamhamedi S. Inherited interleukin-12 deficiency in a child with bacille calmette-guerin and *Salmonella enteritidis* disseminate infection. *J. Clin. Invest.* Vol. 102, No. 12, December 1998,2035-2040.
10. Carlin C, Feldman S, Kruöger J, Menter A, Krueger G. A 50% reduction in the psoriasis area and severity index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. *J Am Acad Dermatol* 2004;50:859-66.
11. Gelfand J, Neimann A, Shin D, Wang X, Margolis D, Troxel A. Risk of myocardial infarction in patients with psoriasis. *JAMA.* 2006;296:1735-1741.
12. McDonald C, Calabresi P. Psoriasis and occlusive vascular disease. *British Journal of Dermatology* (1978) 99,469.
13. Kremers, HM, McEvoy MT, Dann FJ, Gabriel SE. Heart disease in psoriasis. *J Am Acad Dermatol* 2007;57:347-54.
14. Kimball A, Gladman D, Gelfand J, Gordon K, Horn E, Korman N. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. *J Am Acad Dermatol* 10.1016/j.jaad.2008.01.006.

### 9.2 Labeling Recommendations

The labeling recommendations will be added as a review addendum.



---

6. Discuss the potential for malignancy demonstrated by this class of compounds, including the findings from animal studies that indicated an increased carcinogenic risk with inhibition of IL-12/IL23.

Are the members concerned with the potential malignancy demonstrated by this class of compounds, including the findings from animal studies that indicated an increased carcinogenic risk with inhibition of IL-12/IL23?

Yes: 11                      No: 0                      Abstain: 0

Is it important to communicate these findings to prescribers?

Yes: 11                      No: 0                      Abstain: 0

Are additional animal studies needed?

Yes: 1                      No: 9                      Abstain: 1

**Please discuss the relative benefits and risks for the use of ustekinumab in patients with moderate to severe plaque psoriasis:**

7. Do the benefits of ustekinumab therapy in adult patients with moderate to severe psoriasis outweigh the risks?

Yes: 9                      No: 1                      Abstain: 1

8. Do you recommend approval of ustekinumab for the treatment of adult patients with moderate to severe plaque psoriasis?

Yes: 11                      No: 0                      Abstain: 0

a) If the answer is **no**, what additional premarketing studies do you suggest?

i) completion of the pivotal trials extensions prior to approval N/A

ii) new randomized clinical trials N/A

iii) other studies N/A

b) If the answer is **yes**,

i) describe the recommended dosing regimen and the length of treatment

ii) should the product be labeled for patient self administration or only for prescriber administration?

**Self administration: 4**  
**Abstain: 0**

**Prescriber administration only: 7**

iii) are the applicant's risk assessment proposals (PSOLAR, 5 year extension of pivotal trials) sufficient to characterize the long term safety of ustekinumab? Please discuss these options:

a) increasing sample size of PSOLAR.... Is this sufficient?

**Yes: 0**

**No: 11**

**Abstain: 0**

b) epidemiologic study (observational)

c) mandatory registry/restricted distribution

d) disease-based registry

*Comment: While no formal vote was taken, many of the committee members expressed support for a mandatory registry. The meeting adjourned without discussion of a disease-based registry.*

#### 9.4 Subject Selection (Source: protocol for study T08)

##### Inclusion Criteria

1. Be 18 years of age or older at time of consent; may be male or female.
2. Have had a diagnosis of plaque-type psoriasis at least 6 months prior to first administration of study agent (subjects with concurrent psoriatic arthritis [PsA] may be enrolled).
3. Have plaque-type psoriasis covering at least 10% of total BSA at screening and at the time of the first administration of study agent.
4. Have a PASI score of 12 or greater at screening and at the time of the first administration of study agent.
5. Be candidates for phototherapy or systemic treatment of psoriasis (either naive or history of previous treatment).
6. Women of childbearing potential and all men must be using adequate birth control measures (eg, abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) and must agree to continue to use such measures and not become pregnant or plan a pregnancy until 12 months after receiving the last injection of study agent.
7. Able to adhere to the study visit schedule and other protocol requirements.
8. Capable of giving informed consent and the consent must be obtained prior to any study related procedures.
9. Must avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during study.
10. Must agree not to receive a live virus or live bacterial vaccination during the trial or up to 12 months after the last injection.
11. Must agree not to receive a BCG vaccination during the trial or up to 12 months after the last injection.

- d. Within 1 month prior to the first administration of study agent, either have a negative tuberculin skin test, as outlined in Appendix D, or have a newly identified positive tuberculin skin test during screening in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either prior to or simultaneously with the first administration of study agent.
  - e. Have a chest radiograph (both posterior-anterior and lateral views), taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current active TB or old inactive TB.
12. Have screening laboratory test results within the following parameters:
- a. Hemoglobin  $\geq 10$  g/dL
  - b. White blood cells  $\geq 3.5 \times 10^9/L$
  - c. Neutrophils  $\geq 1.5 \times 10^9/L$
  - d. Platelets  $\geq 100 \times 10^9/L$
  - e. Serum creatinine  $< 1.5$  mg/dL (or  $< 133$   $\mu\text{mol/L}$ )
  - f. AST, ALT, and alkaline phosphatase levels must be within 1.5 times the upper limit of normal range for the laboratory conducting the test.
13. Be considered eligible according to the following TB screening criteria:
- a. Have no history of latent or active TB prior to screening.
  - b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
  - c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to or simultaneously with the first administration of study agent.

### Exclusion Criteria

1. Currently have nonplaque forms of psoriasis (eg, erythrodermic, guttate, or pustular).
2. Have current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).
3. Are pregnant, nursing, or planning pregnancy (both men and women) while enrolled in the study.
4. Have used any therapeutic agent targeted at reducing IL-12 or IL-23, including but not limited to CNTO 1275 and ABT-874.
5. Have used any investigational drug within the previous 4 weeks or 5 times the half-life of the investigational agent, whichever is longer.
6. Have used any biologic within the previous 3 months or 5 times the half-life of the biologic, whichever is longer.
7. Have ever received natalizumab or other agents that target alpha-4-integrin.
8. Have received phototherapy or any systemic medications/treatments that could affect psoriasis or PASI evaluation (including, but not limited to, oral or injectable corticosteroids, retinoids, 1,25 dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, or fumaric acid derivatives) within 4 weeks of the first administration of study agent.
9. Have used topical medications/treatments that could affect psoriasis or PASI evaluation (eg, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens) within 2 weeks of the first administration of study agent.

10. Have used any systemic immunosuppressants (eg, MTX, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus) within 4 weeks of the first administration of study agent.
11. Are currently receiving lithium, antimalarials, or intramuscular gold, or have received lithium, antimalarials, or intramuscular gold within 4 weeks of the first administration of study agent.
12. Have received within 3 months prior to the first injection a live virus or bacterial vaccination. Subjects must agree not to receive a live virus or bacterial vaccination during the trial or up to 12 months after the last study agent injection.
13. Have had a BCG vaccination within 12 months of screening. Subject must agree not to receive a BCG vaccination during the trial or up to 12 months after the last study agent injection.
14. Have a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), or open, draining, or infected skin wounds or ulcers.
15. Have or have had a serious infection (eg, sepsis, pneumonia or pyelonephritis), or have been hospitalized or received IV antibiotics for an infection during the 2 months prior to screening.
16. Have a history of latent or active granulomatous infection, including TB, histoplasmosis, or coccidioidomycosis, prior to screening.
17. Have a chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB or fibrosis.
18. Have or ever have had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, *Pneumocystis carinii*, aspergillosis).
19. Have or have had a herpes zoster infection within 2 months of the first administration of study agent.
20. Be known to be infected with human immunodeficiency virus, hepatitis B, or hepatitis C.
21. Have current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease.
22. Have a transplanted organ (with exception of a corneal transplant > 3 months prior to the first administration of study agent).

23. Have a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
24. Have any known malignancy or have a history of malignancy (with the exception of basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to the first administration of study agent).
25. Have been hospitalized in the past 3 years for asthma, ever required intubation for treatment of asthma, currently require oral corticosteroids for the treatment of asthma, or required more than one short-term ( $\leq 2$  weeks) course of oral corticosteroids for asthma within the previous year.
26. Have undergone allergy immunotherapy previously for prevention of anaphylactic reactions.
27. Have shown a previous immediate hypersensitivity response, including anaphylaxis, to an immunoglobulin product (eg, plasma derived or recombinant monoclonal antibody).
28. Be unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.
29. Be known to have had a substance abuse (drug or alcohol) problem within the previous 12 months.
30. Be participating in another trial using an investigational agent or procedure during participation in the trial.

## 9.5 Psoriasis Area and Severity Index (Source: Appendix A of protocol for study T08)

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:

- a. The neck is considered part of the head
- b. The axillae and groin are part of the trunk
- c. 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

## 9.6 Physician's Global Assessment (Source: Appendix of protocol for study T08)

The 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.

**INTERCENTER CONSULTATIVE REVIEW MEMO**

Submitted: March 3, 2008  
Completed: June 26, 2008

To: Maria R. Walsh, Project Manager  
Division of Dermatology and Dental Products/CDER  
HFD-540 (301-796-0852 or 301-796-0944)

From: Rosemary Tiernan, MD, MPH  
Medical Officer  
Division of Vaccines and Related Product Applications  
(DVRPA)/CBER  
HFM-475 (301-827-3070 or 301-827-5984)

**APPROVED**  
By Rosemary Tiernan at 6:51 pm, Jul 14, 2008

Through: R. Douglas Pratt, MD, MPH  
Vaccine Clinical Trials Branch Chief  
Division of Vaccines and Related Product Applications  
(DVRPA)/CBER

**APPROVED**  
By R Douglas Pratt at 7:54 am, Jul 15, 2008

Florence Houn, MD, MPH  
Director, Medical Policy  
Office of Vaccines Research and Review (OVRR)/CBER

Sponsor: Centocor, Inc.  
200 Great Valley Parkway  
Malvern, PA 19355

Product: CNTO 1275 (ustekinumab) Interleukin Inhibitor for Psoriasis (Injection) "First in class/New Molecular Entity" fully human IgG1k monoclonal antibody to human IL-12 p40 that binds with high affinity to human IL-12 and IL-23 and neutralizes their bioactivity preventing these cytokines from binding to their IL-12Rβ1 (IL-12 receptor beta-1) receptor protein expressed on the surface of immune cells. CNTO1275 is a selective immunosuppressant classified according to the proposed Anatomical Therapeutic Chemical Classification system as an Interleukin Inhibitor.

**Summary:**

There are currently 5 FDA approved biologic therapeutics for the treatment of psoriasis: Alefacept (Amevive®), Efalizumab (Raptiva®), Infliximab (Remicade®), Etanercept (Enbrel®), and Adalimumab (Humira®). Amevive® and Raptiva® target the T cell surface receptors CD2 and LFA-1, respectively, and act as T cell immunosuppressive agents. Remicade®, Enbrel®, and Humira® target, and inhibit the cytokine TNFα, an inflammatory cytokine produced during psoriasis. CNTO 1275 has a unique mechanism

of action binding with high affinity to human IL-12 and IL-23 and neutralizing their bioactivity.

**CNT0 1275 (ustekinumab)** is a drug for psoriasis which is currently under review by the Division of Dermatology and Dental products/CDER. A consult was requested of DVRPA regarding this product. CNT0 1275 (ustekinumab) is a fully human IgG1κ monoclonal Antibody to human IL-12 p40 that binds with high affinity to human IL-12 and IL-23 and neutralizes their bioactivity preventing these cytokines from binding to their IL-12Rβ1 (IL-12 receptor beta-1) receptor protein expressed on the surface of immune cells. CNT01275 is a selective immunosuppressant classified according to the proposed Anatomical Therapeutic Chemical Classification system as an Interleukin Inhibitor. The immunosuppression is of prolonged duration because of the product's long-half life of approximately three weeks. The safety and efficacy of this new product was discussed at a CDER Advisory Committee meeting on June 17, 2008. The proposed indication is "treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy." The proposed dose, route and schedule for administration will be as follows:

- patients ≤ 100 kg: initial 45 mg SC dose, followed by a repeat dose 4 weeks later and subsequent doses administered q 12 weeks
- patients > 100 kg: initial 90 mg SC dose, followed by a repeat dose 4 weeks later and subsequent doses administered q 12 weeks.

The Applicant required the following of subjects in the Phase 3 trials used to support licensure:

- "Must agree not to receive a live virus or live bacterial vaccination during the study or up to 12 months after the last injection."
- "Must agree not to receive a BCG vaccination during the study or up to 12 months after the last injection."

Consequently, there is no information available regarding the safety or immunogenicity of concomitant administration of this product with live viral or live bacterial vaccines. In addition, there are minimal data available regarding the safety or immunogenicity of administration of this product when administered with vaccines that are not live (see "Background" section below).

The Applicant proposes the following language to be used in the Warning and Precautions section of their draft labeling:

\_\_\_\_\_

b(4)

CDER provided a link to the electronic NDA 125261 submission for CNT01275 and requested the Division of Vaccines and Related Products Applications (DVRPA) to answer the following questions:

- 1) Please comment on the Applicant's proposed language for the label in light of the conduct of the Phase 3 trials.

**OVRP Revisions for the Precautions section of the label:**

Prior to initiating therapy with [Tradename], psoriatic patients should receive all immunizations appropriate for age as recommended by current immunization guidelines.\* Patients on treatment with [Tradename] should not receive live vaccines.

---

b(4)

**\*Reference regarding vaccination:**

CDC. General Recommendations on Immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006: 55 (No. RR-15).

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5515a1.htm>

- 2) Please comment/advise on how the Applicant should assess the ability of patients to mount an immune response to standard vaccinations, e.g. influenza or pneumococcal vaccine, while under treatment with this product.

The Office of Vaccines Research and Review (OVRP) in CBER does not recommend that the Applicant pursue a study to assess the ability of patients on CNTO 1275 to mount an immune response after vaccination. Please see the sections below for further details regarding the prior history of doing such studies and OVRP's current thinking and reasons to not pursue immune response studies post-vaccination in subjects on immuno-suppressants.

**Background:**

(Information taken from CNTO 1275 FDA briefing document web posted 6-16-08):

<http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4361b1-02-CENTOCOR.pdf>

The Applicant has provided safety data for 2,266 subjects with psoriasis who were treated with ustekinumab. The durations of exposure to the product are reported as follows:

- 1,970 subjects treated for  $\geq 6$  months (994 with 45 mg; 976 with 90 mg)
- 1,285 subjects treated for  $\geq 1$  year (645 with 45 mg; 640 with 90 mg)
- 373 subjects treated for  $\geq 18$  months (187 with 45 mg; 186 with 90 mg)

(Information taken from the CNTO 1275 NDA 125261 submission)

The Sponsor states that a subject's ability to generate a **non-memory B cell antibody** response was evaluated by inoculating subjects with the polyvalent pneumococcal vaccine (a polysaccharide antigen), and then measuring immune titers in these subjects

one month later in three Phase 1 studies (C0379T01, C0379T02 and C0379T03). Results were described by the Applicant as comparable with those expected in a non-immunosuppressed population. Thus, the Applicant believes that at the single time-point examined, B-cell responses to bacterial polysaccharide neo-antigens appeared to be preserved following treatment with CNTO 1275. The data from each of these 3 studies is presented individually below and also combined in a summary table taken from the Applicant's briefing document.

**Study C0379T01**

In Study C0379T01, CNTO 1275 was administered to patients with moderate to severe psoriasis vulgaris as a single dose, 2 hour IV infusion followed by polyvalent pneumococcal polysaccharide vaccine given 72 hours after the CNTO 1275 dose with antibody response measured approximately 4 weeks later. In the past 5 years, these subjects had no prior receipt of polyvalent pneumococcal polysaccharide vaccine. Please see the results depicted in Table 1 below.

**Table 1 Study C0379T01 Results (Response to Pneumococcal Vaccination )**

Study C0379T01 CNTO 1275 Single IV Dose	Antibody response at 4 weeks ( ≥ 2 fold in at least 6 of 12 pneumococcal serotypes)	Negative antibody response to pneumococcal vaccination	Indeterminate antibody response to pneumococcal vaccination	Number of patients in dosing cohort
CNTO 1275 0.09 mg/kg	3	0	1	4
CNTO 1275 0.27 mg/kg	4	0	0	4
CNTO 1275 0.9 mg/kg	3	1	1	5
CNTO 1275 4.5 mg/kg	3	2	0	5
<b>Total</b>	13	3	2	18

(Adapted from Applicant CSR C0379T01 p. 97)

**Medical Officer Comments:**

*Thirteen of 18 subjects with psoriasis, who received one IV dose of CNTO 1275 followed 72 hours later by a polyvalent pneumococcal polysaccharide vaccine mounted a 2 fold or greater IgG antibody response to at least 6 of 12 pneumococcal serotypes at 1 month post vaccination (see Table 1 above). However, no definitive conclusions regarding immune response or protection against disease can be made from this minimal amount of study data. Furthermore, in adults who receive pneumococcal vaccination, the immune correlate of protection remains unknown.*

**Study C0379T02**

In study C0379T02, CNTO 1275 was administered as a single dose subcutaneously (SC) at either 0.27 mg/kg, 0.675 mg/kg, 1.35 mg/kg or 2.7 mg/kg to 18 to 65 year old patients with moderate to severe psoriasis. Subjects, who had not had a pneumococcal vaccine in the past 5 years, received a polyvalent pneumococcal polysaccharide vaccine at 72

hours after their CNT0 1275 dosing and those who had not had a tetanus vaccination within the past 10 years received tetanus toxoid at 72 hours after injection of CNT01275. It is unclear whether these subjects received both tetanus and pneumococcal vaccination concomitantly at 72 hours after dosing with placebo or subcutaneous CNT0 1275. It is unclear exactly which manufactured polyvalent pneumococcal polysaccharide vaccine and tetanus toxoid products were administered to these subjects.

An “acceptable” antibody response at 25 days post pneumococcal vaccination was considered to be greater than or equal to a 2 fold rise in IgG of at least 6 of 12 pneumococcal serotypes (1, 3, 4, 6, 8, 9, 12, 14, 19F, 23F, 51, 56). These pneumococcal serotypes are described as low, intermediate and highly immunogenic pneumococcal serotypes.

**Medical Officer Comments:**

*CBER is not aware of data that supports using a classification scheme for pneumococcal serotypes stratified as “low”, “intermediate” and “highly immunogenic”. It is unclear, regarding which polyvalent pneumococcal polysaccharide vaccine was administered, whether the assay used was a validated IgG ELISA, or whether any of these subjects could have received either a conjugate or polysaccharide pneumococcal vaccination in the distant past i.e. greater than 5 years ago. It is unclear whether the subjects received both tetanus and pneumococcal vaccination concomitantly at 72 hours after dosing with placebo or subcutaneous CNT0 1275 (see Table 2 and Table 3 below)*

**Table 2 Study C0379T02 Results (Response to Pneumococcal Vaccination)**

Study C0379T02 Treatment Arm (Single Subcutaneous Dose)	Antibody Response $\geq$ 2 fold in at least 6 of 12 pneumococcal serotypes	Excluded because of prior receipt of pneumococcal vaccine in past 5 years* or inappropriate sample**	Number of patients in each dosing cohort
CNT0 1275 0.27 mg/kg SC	2/4	1**	5
CNT0 1275 0.675 mg/kg SC	2/3	1**	4
CNT0 1275 1.35 mg/kg SC	2/2	2*	4
CNT0 1275 2.7 mg/kg SC	4/4	0	4
Total CNT0	10/13	4	17
Total Placebo	2/4	0	4

(Adapted from CSR C0379T02, p. 151)

Tetanus has been described as a “recall antigen” because most adults have been vaccinated in the past. Vaccination for tetanus was given 72 hours after CNT0 1275 dosing and antibody assays were performed 25 days after tetanus vaccination. It is unclear whether these subjects also received concomitant polyvalent pneumococcal polysaccharide vaccine. Acceptable antibody levels included a greater than or equal to 4

fold rise in tetanus antibody. In C0379T02, the Applicant states that 5 of 7 (71.4%) evaluable subjects treated with CNTO 1275 and 1 of 2 (50%) subjects treated with placebo had a  $\geq 4$ -fold increase (i.e., positive response) in the post-vaccination tetanus toxoid titer from the pre-vaccine titer (see Table 3 below).

**Table 3 Study C0379T02 Results (Response to Tetanus Vaccination)**

Study C0379T02 Treatment Arm (Single Subcutaneous Dose)	Antibody Response $\geq 4$ fold rise (pre-vaccine to post- vaccine)	Excluded because had received tetanus toxoid in past 10 years* or had inappropriate sample**	Number of patients in each dosing cohort
CNTO 1275 0.27 mg/kg SC	1/2	3* and **	5
CNTO 1275 0.675 mg/kg SC	0/0	4* and **	4
CNTO 1275 1.35 mg/kg SC	1/2	2* and **	4
CNTO 1275 2.7 mg/kg SC	3/3	1*	4
Total CNTO	5/7	10	17
Total Placebo	1/2	2*	4

(Adapted from CSR C0379T02, p.153)

### **Study C0379T03**

Study C0379T03 was a phase 1, double blind, placebo-controlled study evaluating the safety and pharmacology of a single subcutaneously administered dose of CNTO 1275 in subjects with relapsing forms of multiple sclerosis. Subjects, who had not had a pneumococcal vaccine in the past 5 years, received a polyvalent pneumococcal polysaccharide vaccine at 72 hours after their CNTO 1275 dosing and those who had not had a tetanus vaccination within the past 10 years received tetanus toxoid at 72 hours after injection of CNTO1275. It is unclear whether these subjects received both tetanus and pneumococcal vaccination concomitantly at 72 hours after dosing with placebo or subcutaneous CNTO 1275. It is unclear exactly which manufactured polyvalent pneumococcal polysaccharide vaccine and tetanus toxoid products were administered to these subjects. Please see Tables 4 and 5 below.

**Table 4 Study C0379T03 Results (Response to Pneumococcal Vaccination)**

Study C0379T02 Treatment Arm (Single Subcutaneous Dose)	Antibody Response $\geq$ 2 fold in at least 6 of 12 pneumococcal serotypes	Excluded because of prior receipt of pneumococcal vaccine in past 5 years* or inappropriate sample**	Number of patients in each dosing cohort
CNTO 1275 0.27 mg/kg SC	3/4	0	4
CNTO 1275 0.675 mg/kg SC	2/3	1*	4
CNTO 1275 1.35 mg/kg SC	3/4	0	4
CNTO 1275 2.7 mg/kg SC	4/4	0	4
<b>Total CNTO</b>	12/15	1	16
<b>Total Placebo</b>	2/4	0	4

(Adapted from CSR C0379T03, p.175)

**Table 5 Study C0379T03 Results (Response to Tetanus Vaccination)**

Study C0379T02 Treatment Arm (Single Subcutaneous Dose)	Antibody Response $\geq$ 4 fold rise (pre-vaccine to post- vaccine)	Excluded because had received tetanus toxoid in past 10 years* or had inappropriate sample**	Number of patients in each dosing cohort
CNTO 1275 0.27 mg/kg SC	2/2	2*	4
CNTO 1275 0.675 mg/kg SC	1/3	1*	4
CNTO 1275 1.35 mg/kg SC	1/4	0	4
CNTO 1275 2.7 mg/kg SC	3/4	0	4
<b>Total CNTO</b>	7/13	3	16
<b>Total Placebo</b>	3/3	1*	4

(Adapted from CSR C0379T03, p. 176)

**Medical Officer Comments:**

*The number of study subject numbers is too small to allow definitive conclusions. It is unclear whether one would expect a difference in immune response to vaccination in psoriatic patients compared to multiple sclerosis patients. The nature of the underlying disease as well as the treatment options for psoriasis and multiple sclerosis may impact the immune response differently and it may not be reasonable to combine immune response data for these two different patient populations. Furthermore, there is lack of appropriate control arms to evaluate immune response to inactivated vaccines such as an arm of psoriasis subjects not on CNTO 1275 and a comparator arm with healthy*

*subjects. Additional studies evaluating immune response after vaccination must utilize immune response assays that have been validated. However, please see our discussion below regarding CBER concerns that doing studies to assess immune response post vaccination in patients with autoimmune diseases on immunomodulatory or immunosuppressant drugs may not provide useful data and instead the results may mislead some to assume mounting a similar immune response to that found in a healthy patient infers protection against infection or disease.*

See the Summary “Table 4” below which captures the immune response data in the three Phase 1 studies of subjects who received single dose CNTO 1275 followed by polyvalent pneumococcal polysaccharide vaccine and tetanus toxoid (Table 4 was taken from the Applicant’s briefing document (page 39) web posted as of 6-16-08) <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4361b1-02-CENTOCOR.pdf>

<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%)

**Summary Medical Officer Comments:**

**General Comments**

*There is no information in this BLA regarding the administration of CNTO 1275 with live vaccines such as live viral vaccines or live bacterial vaccines. Live vaccines should not be administered to patients on this immunosuppressant because there is a possibility that the infectious live agent, although it may be attenuated, may cause disease in the immunosuppressed patient, and this needs to be clearly stated in the label for CNTO 1275.*

*In addition, the limited amount of immunogenicity data presented in the Applicant’s summary table above (Table 4 from page 39 of the Applicant briefing document) will not be adequate to include in the label as a description of the safety and immunogenicity of administration of CNTO 1275 with pneumococcal polysaccharide vaccine and/or tetanus toxoid. The pneumococcal and tetanus vaccines were given to a small number of subjects with different underlying diseases (either psoriasis or multiple sclerosis) using different routes of administration (IV or SC) and did not utilize the final proposed CNTO 1275 dosing schedule but rather these subjects*

*received only a single dose of CNTO 1275. It is unclear whether one would expect a difference in immune response to vaccination in psoriatic vs multiple sclerosis patients, although the Applicant assumes that the immune responses will be similar. The nature and severity of the underlying disease as well as the spectrum of treatment options utilized for psoriasis and multiple sclerosis prior to a course of CNTO-1275 may impact the immune response to vaccination differently. For pneumococcal vaccination in adults, there is no accepted immune correlate of protection. Consequently, there remains a question regarding which biomarkers to measure and what immune response to achieve post vaccination because the immune response necessary to demonstrate disease protection has not yet been determined in healthy adults.*

*CBER does not think that meaningful data will result from conducting immune response studies after vaccination in subjects receiving immunosuppressants such as CNTO 1275. CBER concerns include that Sponsors, who use approved vaccines as diagnostic agents in immunosuppressed subjects, may find the level of immune response measured post-vaccination is similar to that elicited in a normal host and infer that the subject has intact B cell function and protection against infection and/or disease. Sponsors may also try to use these small immunogenicity studies post-vaccination to make competitive label claims that their immunosuppressant selectively impacts a particular arm of the immune system in order to effectively treat autoimmune disease while "preserving" humoral immune response after vaccination.*

*Antibody response measured in ELISA assays post vaccination may not correlate with protection against disease. For tetanus there is an antibody immune correlate of protection, but the level of immune response that would be protective in a subject treated with immune modulating drugs remains unknown. For pneumococcus, there is no immune correlate of protection in adults. Licensure of pneumococcal polysaccharide vaccines (PPV) in children and adults was based on demonstration of clinical efficacy in the prevention pneumococcal disease. Although an immunologic correlate of protection against disease for pneumococcal polysaccharide vaccines has not been established, most healthy adults, including the elderly, demonstrate at least a 2-fold rise in pneumococcal type-specific IgG antibody within two to three weeks of immunization [PDR 55<sup>th</sup> ed, p1671]. Thus, while a 2-fold rise in IgG antibody has not been correlated with protection, this immune response is observed following the receipt of a 23-valent PPV in healthy adults. In clinical studies with Pnu-Imune 23<sup>®</sup>, more than 90% of all adults showed two-fold or greater increase in geometric mean antibody titer for each capsular type contained in the vaccine [PDR 55<sup>th</sup>, p1671]. Antibody response rates to a PPV have been used in the published literature as a marker of B cell function [Rubins JB et al. Infect Immun 1999; 67:5979-5984]. Subjects with impaired immune function have shown diminished antibody responses to PPV. Nevertheless, PPVs are not approved for assessing immune status and, in particular, B-cell function in individuals or groups of subjects. Data to validate responses to the vaccine as a marker of B-cell function have not been provided and, the sensitivity and specificity of this method is not known.*

*Although it is a different clinical setting, it should be noted that at present there is ongoing discussion in the allergy and immunology community regarding the criteria to use when trying to identify patients with immunodeficiency by assessment of humoral immune competence after vaccination (“diagnostic vaccination”). No vaccine is approved for such a diagnostic indication.*

*While CBER does ask companies to perform vaccine-vaccine interaction studies regarding concomitant vaccination in healthy adults and healthy children using immune endpoints powered to detect pre-specified differences, these studies are conducted after efficacy of the primary vaccine has been established and antibody or other immune response has been gathered from the efficacy trial. While these data may not be sufficient to establish retrospectively a correlate of protection, these immune response data are evaluated in the context of the efficacy study. Studies of immune response post vaccination in subjects with autoimmune diseases on immunosuppressant drugs do not have such clinical data on vaccine efficacy.*

#### **CBER Past and Current Thinking**

*(This information below captures recent discussion with OTRR and OVRR staff)*

##### **Past /History:**

In the past, OTRR/CBER asked Sponsors to conduct vaccine studies to determine whether tumor necrosis factor (TNF) blockers inhibited B cell responses. OTRR/CBER requested a study of a **B cell dependent antigen** and Sponsors studied pneumococcal polysaccharide vaccine. When studies to evaluate the effects of TNF blockers on **T cell dependent antigens** were requested, the manufacturers studied responses to trivalent inactivated influenza vaccination. When the first manufacturer submitted the results they asked to put the results in their label. OTRR debated whether this was appropriate and had many discussions with “pro and con” views presented. The Office of Vaccines Research and Review (OVRR) was consulted at the time. In the end, it was decided that since clinicians routinely vaccinate their patients on TNF blockers that it would be worthwhile to present the information learned from the randomized, controlled clinical trials of response to vaccination. The description of study results were crafted in language to avoid suggesting that vaccination would produce similar protection from infection as vaccination would in a person not receiving TNF blockers. The labels for immunosuppressants used for rheumatoid arthritis (RA) such as Enbrel®, Humira®, Kineret® and Orencia® include results reported for responses to vaccination. Similar concerns regarding labeling for other immunomodulatory drugs such as the interferons have been considered. In labeling, OTRR stated that the wording was carefully couched so as to not encourage the impression that vaccine efficacy was unchanged, and certainly that there was no valid conclusions from any cross-product-labeling comparison. No Advisory committees suggested doing these immune response studies of vaccination in patients receiving immunosuppressant or immunomodulatory drugs.

OTRR/CBER was concerned that the populations who might take these biologic products on a chronic basis (e.g., older adults with rheumatoid arthritis (RA) or children with RA)

who need to get certain routine vaccinations might in fact not be adequately protected because of an inability to mount an appropriate response to whatever vaccination they receive. OTRR had hoped that studies assessing immune responses to standard vaccines among patients who are taking these drugs might increase the understanding regarding if or what types of cellular or humoral defects exist.

Successive discussions between OTRR and OVRR led to the conclusion that unless there was frank failure of an expected response (or component of response), we really had little basis to interpret the results. If it were critical to understand the vaccine efficacy in the face of concomitant immunosuppressant/immunomodulator drug, it would be necessary to obtain results from a large-efficacy trial and this was not going to be obtainable since the basis of concern did not justify that level of burden for a post-marketing study.

Over the years, CBER has continued to provide comments for post-marketing studies that CDER divisions requested regarding concomitant or staggered administration of vaccines with immunosuppressant drugs to treat autoimmune diseases. Such studies have often been insufficient in size, scope and design to ultimately allow a label change that supports that there is no interference when a vaccine is concomitantly administered with an immunosuppressant. Patients on immunomodulatory or immunosuppressant drugs, who receive vaccines to prevent infectious disease and are able to mount immune responses similar to that found in normal healthy hosts, may still not be protected against developing infection and disease. The immune response measured after vaccination may not be a correlate for protection. A clinical efficacy trial may ultimately be necessary to demonstrate that this "normal" immune response after vaccination in the host receiving an immunosuppressant drug is still sufficient to provide protection for the immunosuppressed host. Conduct of such a trial may not be feasible due to the variable spectrum of age and underlying autoimmune disease necessitating different schedules for immunosuppressant drug dose and administration as well as different concomitant medications and co-morbidities in these subject populations.

#### **Current Thinking**

In CBER, several different types of post-vaccination immune response studies are conducted including:

- 1) immune response measured in the context of an efficacy study understanding that it is not always possible to determine that the measured immune response is a correlate of protection
- 2) immune response that is measured to demonstrate consistency across manufactured vaccine lots
- 3) immune response that is used in bridging studies, e.g., for a new population or age group or for comparison between products
- 4) immune response to determine that there is no interference with immune response when vaccines are concomitantly administered ("vaccine-vaccine interaction").

However, CBER plans to further discuss with CDER divisions the limited value in requesting companies to do pre or post-marketing studies ("vaccine-drug interaction") evaluating immune response after vaccination in complex patient populations with a

broad spectrum of underlying diseases, age and co-morbidities who are maintained on immunomodulatory drug treatment regimens of varying dose and duration.. CBER does not encourage that such immune response studies post vaccination be requested of the Sponsors of these immunosuppressant drugs because these studies do not yield useful data and Sponsors may attempt to leverage the questionable results into competitive label claims.

It is unclear whether such pre-or post-marketing immune response studies can ever adequately address concerns regarding interference of the immunosuppressant with response to vaccination and it may be an unreasonable commitment of time, effort and money to request companies to do such studies until there is more clear consensus regarding how to best evaluate and correlate immune response with clinical efficacy in the immunosuppressed host.

These immune response studies post-vaccination and conducted to date, do not provide useful data that could be included in a product label to guide clinicians in their medical practice. Currently, practitioners who treat patients with autoimmune disease requiring immunosuppressant drugs may refer to the 2006 Advisory Committee on Immunization Practices (ACIP) guidance (see excerpt below):

**CDC. General Recommendations on Immunization:** recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006; 55(No.RR-15).

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5515a1.htm>

***Other Immunosuppressive Drugs***

Whenever feasible, clinicians should provide all indicated vaccines to all persons before initiation of chemotherapy, before treatment with other immunosuppressive drugs, and before radiation or splenectomy. Persons receiving chemotherapy or radiation for leukemia and other hematopoietic malignancies, solid tumors, or after solid organ transplant should be assumed to have altered immunocompetence. **Live-attenuated vaccines should not be administered for at least 3 months after such immunosuppressive therapy. Inactivated vaccines administered during chemotherapy might need to be readministered after immune competence is regained.**

Persons vaccinated before chemotherapy for leukemia, lymphoma, other malignancies, or radiation generally are thought to retain immune memory after treatment, although revaccination following chemotherapy for acute lymphoblastic leukemia might be indicated (139).

Revaccination of a person after chemotherapy or radiation therapy is not thought to be necessary if the previous vaccination occurred before therapy and not during the therapy, with the exception of recipients of HSCT, who should be revaccinated as recommended previously. Determination of the level of immune memory and the need for revaccination should be made by the treating physician. Inactivated vaccines can be administered during low dose intermittent or maintenance therapy of immunosuppressive drugs. The safety and efficacy of live-attenuated vaccines during such therapy is unknown. Physicians should carefully weigh the risks for and benefits of providing injectable live vaccines to adult patients on low-dose therapies for chronic autoimmune disease. The safety and efficacy of live-attenuated vaccines administered concurrently with recombinant human immune mediators and immune modulators is unknown. **Evidence that use of therapeutic monoclonal antibodies, especially the antitumor necrosis factor agents adalimumab, infliximab, and etanercept, causes reactivation of latent tuberculosis infection and tuberculosis disease and predisposes to other opportunistic infections suggests caution in the use of live vaccines in patients receiving these drugs (105–110).** Until additional information becomes available, avoidance of live attenuated vaccines during intermittent or

low dose chemotherapy or other immunosuppressive therapy is prudent, unless the benefit of vaccination outweighs the hypothetical increased risk for an adverse reaction after vaccination.

---

**OVRP Conclusions/Recommendations:**

- 1) Revise the Precautions section of the CNTO 1275 label as follows:

Prior to initiating therapy with [Tradename], psoriatic patients should receive all immunizations appropriate for age as recommended by current immunization guidelines.\* Patients on treatment with [Tradename] should not receive live vaccines. Vaccinations that are not live and are received during a course of [Tradename] may not elicit an immune response sufficient to prevent disease. Caution is advised when administering live vaccines to household contacts of patients receiving [TRADENAME] because of the potential risk for shedding and transmission.

**\*Reference regarding vaccination:**

CDC. General Recommendations on Immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006: 55 (No. RR-15).

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5515a1.htm>

- 2) The Office of Vaccines Research and Review (OVRP) in CBER does not recommend that the Applicant pursue a post-marketing study to assess the ability of patients on CNTO 1275 to mount an immune response after vaccination. Post-vaccination immune response studies conducted in patient populations with underlying autoimmune diseases receiving immunosuppressant drugs ("vaccine-drug interaction") have not provided useful data that should be included in a product label to guide clinicians in their medical practice and in fact such information may mislead clinicians to assume that the vaccinated patient is protected against infection or disease when this may not actually be the case. It is unlikely that it would be feasible to conduct clinical efficacy trials to evaluate whether immune response post-vaccination in subjects on CNTO 1275 is protective considering the variables related to underlying immune status of the patient as well as prior vaccination history, exposure and immunity to infectious diseases and different dose regimens and schedules for the immunosuppressant drugs. Regarding vaccination with the pneumococcal polysaccharide vaccines, there is a concern in healthy adults that repeat vaccination may actually cause "hypo-responsiveness" to pneumococcal polysaccharide and studies should not be done using these products in patients on immunosuppressants, who already may have a compromised ability to respond to vaccination, as this may be an added risk if a need for re-vaccination develops in the future. Finally, it will be important for the Applicant and the CDER Dermatology Division to collaborate on active post-marketing studies and passive post marketing surveillance in order to capture and characterize infectious disease adverse events that occur with the use of CNTO1275.