

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**125261**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## BIOLOGICS LICENSING APPLICATION

### CLINICAL STUDIES

**NDA/Serial Number:** 125261 / 0 (Resubmission after CR)  
**Drug Name:** STELARA (ustekinumab)  
**Indication(s):** Psoriasis  
**Applicant:** Centocor  
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**Review Priority:** Standard review

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## Table of Contents

<b>1</b>	<b>EXECUTIVE SUMMARY .....</b>	<b>3</b>
1.1	Conclusions and Recommendations.....	3
1.2	Brief Overview of Clinical Studies .....	3
1.3	Statistical Issues and Findings.....	4
<b>2</b>	<b>INTRODUCTION .....</b>	<b>4</b>
2.1	Overview .....	4
2.2	Data Sources .....	6
<b>3</b>	<b>STATISTICAL EVALUATION .....</b>	<b>6</b>
3.1	Evaluation of Efficacy.....	6
3.1.1	Study Design and PGA .....	6
3.1.2	Evaluation of Modified PGA Scores .....	9
3.1.3	Discussion of Findings.....	10
3.2	Evaluation of Safety .....	11
<b>4</b>	<b>FINDINGS IN SPECIAL/SUBGROUP POPULATIONS .....</b>	<b>11</b>
4.1	Gender, Race, and Age .....	11
4.2	Other Special/Subgroup Populations.....	11
<b>5</b>	<b>SUMMARY AND CONCLUSIONS .....</b>	<b>11</b>
5.1	Statistical Issues and Collective Evidence.....	11
5.2	Conclusions and Recommendations.....	12
	<b>SIGNATURES/DISTRIBUTION LIST.....</b>	<b>12</b>

## 1 Executive Summary

### 1.1 Conclusions and Recommendations

The original application for Stelara (ustekinumab) was issued a Complete Response letter in December 2008 due to product quality issues and the need for a Risk Evaluation and Mitigation Strategy (REMS). In addition to addressing those issues in this re-submission, the applicant has submitted proposed modified labeling in which the Physician's Global Assessment (PGA) response rates were slightly different than the response rates submitted in the original application. The applicant stated that the results were modified after an EMEA inspection identified that an investigator was deviating from the protocol. The inspection noted that Dr. Kim Papp (Waterloo, Ontario, Canada), who participated in both Studies 08 and 09, recorded PGA outcomes based on his overall clinical impression, rather than from the protocol-specified method of reporting the value calculated from the average of induration, erythema, and scaling scores. After 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 PGA score modifications led to a net reduction in PGA success rates of 0 to 1% in each arm of each study. The original and modified PGA success rates are presented in Table 1. The modified Week 12 PGA results may be used in labeling.

**Table 1 - Original and Modified PGA Success Rates at Week 12 (Studies 08 and 09)**

	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%)

### 1.2 Brief Overview of Clinical Studies

The applicant has conducted two Phase 3 placebo-controlled studies (08 and 09) to support the safety and efficacy of ustekinumab 45 mg and 90 mg for the treatment of adults with chronic moderate to severe psoriasis who are candidates for phototherapy or systemic therapy. The timepoint for primary efficacy assessment was Week 12. The protocol-specified primary efficacy endpoint was PASI 75 response and the principal secondary endpoint was a score of clear or minimal on the Physician's Global Assessment. At Week 12, subjects randomized to placebo were crossed over to active treatment with ustekinumab and were to be followed for up to 5 years on various maintenance therapy regimens. Refer to the original statistical review for a full description of the clinical studies. This review will focus only on the applicant's proposed

changes to the PGA response rates as a result of EMEA inspection finding that Dr. Papp was using a non-protocol method of assessing PGA scores. Dr. Papp participated in both studies, enrolling 32 out of 766 subjects (4%) in Study 08 and 52 out of 1230 subjects (4%) in Study 09.

### **1.3 Statistical Issues and Findings**

The changes in the PGA scores impacted relatively few subjects in Studies 08 and 09 (12 out of 766 subjects in Study 08 and 16 out of 1230 subjects in Study 09). The response rates for each arm either remained the same or dropped by approximately 1% after the PGA scores were modified, leading to identical conclusions as with the original reported values as the results retained statistical significance. The modifications are based on information recorded on the PGA worksheets that were filled out at the time the data was collected. However, instead of transcribing the information from the worksheet, the investigator entered a different value for the PGA into the CRF if he felt that another value better reflected his clinical impression of the subject. Thus the modifications are based on source information maintained at the investigational site, but not originally recorded directly on the CRF. However, since the original worksheets are available to the applicant, it is appropriate to adjust the PGA scores to conform to the intention of the protocol and the method used by the other investigators in the study, and present results based on the modified values.

Since the previous database lock, four subjects in Study 08 transferred sites. Under the applicant's subject numbering system, subjects are assigned new subject numbers when they transfer, and only the most recently assigned subject number is retained in the electronic database. The subjects with re-assigned subject numbers include one subject who was treated by Dr. Papp during the initial weeks of the study. The information regarding the previously assigned subject numbers and investigators is not included in the electronic datasets, but is only available in the supplementary text provided by the applicant. The available databases do not directly permit the reviewer to match subjects who transfer sites in the middle of the study visit-wise to all investigators responsible for their treatment and assessment. The applicant should be encouraged to design future studies with extended follow-up with a subject tracking system that maintains a unique subject ID even when subjects transfer from one site to another, rather than assigning new subject numbers at the new site.

## **2 Introduction**

### **2.1 Overview**

BLA 125261 / 0 for STELARA (ustekinumab) for the treatment of psoriasis was originally submitted to the Agency on 11/29/2007. The Agency issued a Complete Response (CR) letter on 12/18/2008 due to product quality deficiencies and the need for a Risk Evaluation and Mitigation Strategy (REMS). Labeling negotiations were deferred until the issues in the CR letter were addressed. On 1/9/2009, the applicant submitted their response to the issues in the CR letter, initiating a new review cycle. As part of the resubmission, the applicant submitted revised labeling that included changes to the

Physician's Global Assessment response rates from the clinical studies. To justify the changes, the applicant referred to information originally submitted to the FDA on 10/28/2008 (sequence number 44), which was submitted near the end of the initial review cycle and therefore not reviewed. This submission stated

*An EMEA GCP pre-approval inspection of Dr Papp's site for the PHOENIX 2 (C0743T09) study discovered errors in the calculation of Physicians Global Assessment (PGA) scores for some subjects enrolled at the site. It was subsequently noted that the calculation errors also affected some subjects in the PHOENIX 1 study. These data have been corrected and the subjects' PGA scores were revised in the eCRF. [pg 2 of file c0743t09-report-body-28wk-addendum.pdf, in sequence number 44]*

Additional details about the PGA problems at this site were requested from the applicant on 2/23/2009. In response the applicant stated

*During the EMEA inspection at the site of Dr. Papp for C0743T09, the inspectors observed that the site did not regularly follow the protocol when entering the Physicians Global Assessment (PGA) score in the eCRF based on a misunderstanding of the principal investigator regarding how to score the PGA. The investigator accurately assessed and scored each component of the PGA (induration, erythema, and scaling), accurately totaled the subcomponents, and accurately calculated and recorded the PGA on the worksheets. However, if the calculated PGA did not agree with his overall assessment of the subject's PGA, he used clinical judgment in adjusting the final PGA entered into the eCRF.*

*The following corrective actions were undertaken and completed by June 2008:*

- Data from the site for both C0743T08 and C0743T09 were corrected to reflect the original, accurate calculation (i.e. not the investigator's adjusted PGA), and the data were monitored (June 2008) by the CRA to ensure accurate transcription from the source documentation (ie, the worksheets) to the eCRF.*
- CRAs monitoring all other sites were queried (May 2008) to determine if any other PI or sub-investigator performed the PGA assessment incorrectly. All other study site personnel were reported to be completing the PGA according to the protocol. [pg 9-10 of file coverletter.pdf of sequence number 54]*

One additional wrinkle to the analysis of the revised PGA scores is that the applicant reports that 4 subjects in Study 08 have been re-assigned different subject numbers in the revised datasets from the original datasets. The applicant reports that in each case, this is due to the subjects transferring sites between the Week 52 database lock (the original datasets) and the Week 76 database lock (the revised datasets) for that study. After subjects transferred sites, they were assigned new subject numbers at their new sites. The database retains only reference to the most recent subject number, not the subject/site number in effect during the first 52 weeks of the study; however, the applicant has provided a table within their cover letter (sequence number 54) indicating the subject numbers (before and after the transfer) of the affected subjects. Of note, one of the four subjects (108-023) was originally enrolled at Dr. Papp's site, and needs to be considered in the re-analysis of PGA scores. The following subjects (Table 2) were reassigned subject numbers due to site transfer in the Week 76 database for Study 08.

**Table 2 – Subjects Reassigned Subject Numbers Due to Site Transfer after Week 52 in Study 08**

Original ID (Week 52 Database)	Reassigned ID (Week 76 Database)
034-044	019-011
021-008	020-012
102-012	107-032
108-023	106-022

This review will focus on the applicant's proposed changes (through Week 12 only) to the PGA scores based on the EMEA inspection of Dr. Papp's sites in Studies 08 and 09 (Site 108 in Study 08 and Site 013 in Study 09).

## 2.2 Data Sources

This reviewer evaluated the sponsor's cover letters and amended clinical study reports, as well as the proposed labeling from sequence numbers 44 (initial notice of change in PGA results dated 10/28/2008), 53 (BLA resubmission, dated 1/9/2009), and 54 (response to FDA request for more information on the revised scores and datasets, dated 3/5/2009). This submission was submitted in eCTD format and was entirely electronic. The revised datasets used in this review are archived at \\Cbsap58\M\CTD\_Submissions\STN125261\0054\m5\datasets.

## 3 Statistical Evaluation

### 3.1 Evaluation of Efficacy

#### 3.1.1 Study Design and PGA

The efficacy of ustekinumab is supported by two Phase 3 studies, Studies 08 and 09. The primary efficacy timepoint was Week 12, and the studies each had 3 arms during the initial 12-week period: 45 mg ustekinumab, 90 mg ustekinumab, and placebo. Subjects received treatment injections at baseline and Week 4. The primary efficacy endpoint was PASI 75 at Week 12. The first major secondary endpoint was a score of clear or minimal on the PGA at Week 12. The Agency has considered PGA response an important endpoint from psoriasis trials to convey in labeling. For a detailed description of the study design and results refer to the original statistical review. This review will focus on the sponsor's changes to the PGA data (from baseline to Week 12 only) from the initial submission to the current submission. All PASI efficacy data remains unchanged.

The scale for the Physician's Global Assessment (PGA) is as follows. This information was to be completed on a worksheet (assessing and averaging induration, erythema, and scaling scores), with the final result recorded in the eCRF. The worksheets are not included with the eCRFs.

**Physician's Global Assessment**

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.

The PGA success rates at Week 12 (ITT) for Studies 08 and 09, as they were submitted in the original application, are presented in Table 3. These results were confirmed by this reviewer based on the datasets submitted to the Agency.

**Table 3 – Original Efficacy Results - PGA Cleared or Minimal at Week 12**

	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
<b>Study 08</b>	N=255	N=256	N=255
	154 (60%)	158 (62%)	10 (4%)
	p<0.001	p<0.001	
<b>Study 09</b>	N=409	N=411	N=410
	278 (68%)	302 (73%)	20 (5%)
	p<0.001	p<0.001	

The ustekinumab studies submitted to the FDA were also being reviewed by the European Medicines Agency (EMA) concurrently. The applicant was notified by the EMA that an inspection of Site 013 in Study 09 (Dr. Papp, Waterloo, Ontario) revealed that although the investigator was correctly filling out the PGA worksheet, if the investigator did not believe that the calculated PGA score from the worksheet matched the investigator's clinical impression of the subject's disease status, the investigator reported a PGA score in the CRF representing his clinical impression rather than the value calculated from the worksheet. This investigator was also the principal investigator at Site 108 in Study 08, and used the same procedure to record the PGA for subjects in that study. After being notified of this protocol violation, the applicant queried its internal monitors for the other sites to see if any other investigators were incorrectly recording the PGA scores. The monitors did not identify any other sites that were violating the protocol in this manner. The applicant then updated the eCRFs and datasets with the information recorded on the PGA worksheets from Dr. Papp's sites and re-ran the analyses.

The modified 12-week data led to a net loss of 5 PGA responders in Study 08 (3 on the 45 mg arm and 2 on the 90 mg arm), and a net loss of 5 PGA responders in Study 09 (1 on the 45 mg arm, 2 on the 90 mg arm, and 2 on the placebo arm). The original and modified PGA response rates from Dr. Papp's sites in the two studies are presented in Table 4.

**Table 4 – Original and Modified Efficacy Results at Dr. Papp's Sites (PGA Cleared or Minimal at Week 12)**

	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
<b>Study 08</b>	N=12	N=10	N=10
Original	9 (75%)	5 (50%)	1 (10%)
Modified	6 (50%)	3 (30%)	1 (10%)
<b>Study 09</b>	N=17	N=18	N=17
Original	12 (71%)	13 (72%)	2 (12%)
Modified	11 (65%)	11 (61%)	0 (0%)

The changes reduced the success rates on each arm for the whole study by 1% or less, and did not materially impact the p-values. The modified efficacy results are presented in Table 5. The applicant has proposed using the modified PGA response rates in labeling.

**Table 5 – Modified Efficacy Results - PGA Cleared or Minimal at Week 12**

	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
<b>Study 08</b>	N=255 151 (59%) p<0.001	N=256 156 (61%) p<0.001	N=255 10 (4%)
<b>Study 09</b>	N=409 277 (68%) p<0.001	N=411 300 (73%) p<0.001	N=410 18 (4%)

### 3.1.2 Evaluation of Modified PGA Scores

In Study 08, Dr. Papp enrolled 32 subjects: 12 were randomized to 45 mg, 10 were randomized to 90 mg and 10 were randomized to placebo. After the Week 12 scores were modified to match the PGA worksheet, 20 subjects had scores which remained the same, 6 had higher (worse) scores and 6 had lower (better) scores. Of the 6 subjects with worse scores, 5 moved from PGA scores of 1 (success) to 2 (failure). The remaining subject moved from a PGA score of 0 to 1 and was classified as success under both cases. The 6 subjects whose scores improved moved either from a 3 to a 2 or a 4 to a 3, and thus were failures under both cases. The worksheet scores and the initially reported clinical impression scores for Dr. Papp's site in Study 08 are presented in Table 6 (cells where the PGA response value was modified are highlighted).

**Table 6 – Crosstabulations of Clinical Impression PGA Scores (Original Values) and Worksheet PGA Scores (Modified Values) at Week 12 at Site 08-108**

Clinical Impression	45 mg Worksheet					90 mg Worksheet					Placebo Worksheet				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
	0	2					0	1	1			0			
1		4	3			1		1	2		1	1			
2				2		2			4		2		1		
3				1		3			1		3		3	3	
4						4					4			2	

Note: Bolded counts represent the subjects reclassified from success to failure ( $S \rightarrow F$ ). Success is defined as a score of 0 or 1.

In Study 09, Dr. Papp enrolled 52 subjects: 17 were randomized to 45 mg, 18 were randomized to 90 mg and 17 were randomized to placebo. After the Week 12 scores were modified to match the PGA worksheet, 35 subjects had scores which remained the same, 7 had higher (worse) scores and 9 had lower (better) scores, and 1 subject was not evaluated (missing at Week 12). Of the 7 subjects with worse scores, 6 moved from PGA scores of 1 (success) to 2 or 3 (failure). The remaining subject moved from a PGA score

of 0 to 1 and was classified as success under both cases. Of the 9 subjects whose scores were changed to better scores, 1 subject moved from 2 (failure) to 1 (success). On the 45 mg arm, 2 subjects changed from success to failure and 1 subject changed from failure to success, leading to a net loss of 1 success on this arm. The remaining 8 subjects whose scores improved moved remained classified as failures after the modification. The subject with the missing Week 12 score was classified as a failure. The worksheet scores (modified values) and the initially reported clinical impression scores for Dr. Papp's site in Study 09 are presented in Table 7.

**Table 7 - Crosstabulations of Clinical Impression PGA Scores (Original Values) and Worksheet PGA Scores (Modified Values) at Week 12 at Site 09-013**

Clinical Impression	45 mg Worksheet					90 mg Worksheet					Placebo Worksheet				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
	0	4	1	<i>S→F</i>			3		<i>S→F</i>			0			<i>S→F</i>
1		5	<i>I</i>	<i>I</i>		1	8	<i>I</i>	<i>I</i>		1		2		
2			<i>I</i>	4		2		3			2		3		
3		<i>F→S</i>				3			1		3		5	4	
4						4			1		4		1	1	

Note: Bolded counts represent the subjects reclassified from success to failure (*S→F*) or failure to success (*F→S*). Success is defined as a score of 0 or 1.

In general it appears that the subjects receiving ustekinumab were more likely to have their PGA scores worsened upon rescoring, while placebo subjects were more likely to have their PGA scores improved. Thus the modified scores ultimately brought the means of the PGA scores of ustekinumab and placebo slightly closer together.

### 3.1.3 Discussion of Findings

The changes in the PGA response classification impacted relatively few subjects in Studies 08 and 09 (12 out of 766 subjects in Study 08 and 16 out of 1230 subjects in Study 09, or about 1.4% of subjects). The response rates for each arm either remained the same or dropped by approximately 1% after the PGA scores were modified, leading to identical conclusions as with the original values. The modifications are based on information recorded on the PGA worksheets that were filled out at the time of the data collection, but instead of transcribing the information from the worksheet, the investigator entered a different value for the PGA into the CRF if the investigator felt that another value better reflected his clinical impression of the subject. Thus the modifications are based on source information maintained at the investigational site, but not originally recorded directly on the CRF. However, since the original worksheets are available to the applicant, it is appropriate to adjust the PGA scores to conform to the intention of the protocol and the method used by the other investigators in the study, and present results based on the modified values.

While it is encouraging that some subjects were able to transfer sites, when presumably the alternative would have been for the subjects to discontinue the study and not provide follow-up information in these 5-year studies, I am concerned with the fact that transferring subjects receive new subject ID numbers and the database does not keep

track of which investigators were responsible for which visits for transferring subjects. In Study 08, one subject from Dr. Papp's site later transferred to a different site, and was assigned a new subject ID. From the database itself, it is not possible to link this subject back to Dr. Papp without the supplemental information provided by the applicant in the text. As Studies 08 and 09 are ongoing 5-year studies that will continue to accrue safety information, being able to link all subjects to the investigators who evaluated them could be important. In the future, the applicant should be encouraged to use a subject tracking system that does not require subject IDs to be manually changed (losing prior information) and allows subjects who transfer sites in the middle of the study to be matched visit-wise to all investigators responsible for their treatment and assessment.

### **3.2 Evaluation of Safety**

Refer to original review.

## **4 Findings in Special/Subgroup Populations**

### **4.1 Gender, Race, and Age**

Refer to original review.

### **4.2 Other Special/Subgroup Populations**

Refer to original review.

## **5 Summary and Conclusions**

### **5.1 Statistical Issues and Collective Evidence**

One investigator (Dr. Papp, Waterloo, Ontario) who participated in both Studies 08 and 09 recorded PGA outcomes based on his overall clinical impression, rather than the value calculated from the average of induration, erythema, and scaling scores, as was specified in the protocol. This inconsistency with the protocol was identified during an EMEA inspection of Dr. Papp's site. The worksheet PGA scores were recorded and maintained in the source documentation at the site. The applicant has updated the datasets in this submission with the PGA values from this site recorded as per the protocol using the worksheet values. The applicant has stated that other investigators were queried and all others reported reporting PGA scores per the protocol.

Among the subjects whose Week 12 PGA scores were different under the two scoring methods, similar numbers of subjects improved (15) and worsened (13). However, among subjects whose modified scores led to a change in success/failure classification, most changes led to subjects being reclassified as failures, with 11 subjects changing from success to failure and only 1 subject changing from failure to success. The modified scores led to a net reduction in the PGA success rates of 0 to 1% in each arm of each study. The original and modified PGA success rates are presented in Table 8. The overall efficacy conclusions (that efficacy of ustekinumab has been demonstrated) are unchanged.

**Table 8 – Original and Modified PGA Success Rates at Week 12**

	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%)

### 5.2 Conclusions and Recommendations

The use of source document information (worksheets) to modify the values of the PGA score at Dr. Papp's sites in Studies 08 and 09 to conform to the intent of the protocol does not alter the efficacy conclusions of Studies 08 and 09, which demonstrated that ustekinumab is effective in the treatment of psoriasis. The modifications led to a net reduction in PGA success rates of 0 to 1% in each arm of each study. The modified Week 12 PGA results may be used in labeling.

The applicant should be encouraged to design future studies with extended follow-up with a subject tracking system that maintains a unique subject ID even when subjects transfer from one site to another, rather than assigning new subject numbers at the new site. This would allow subjects who transfer sites in the middle of the study to be matched visit-wise to all investigators responsible for their treatment and assessment, which could be important for long-term efficacy and safety evaluation. One subject in Study 08 treated at Dr. Papp's site in the initial study period was not linked to Dr. Papp in the current database, because the subject's ID number was changed when the subject later switched to another investigator's site.

### Signatures/Distribution List

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Date: 4/30/2009

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U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## BIOLOGICS LICENSING APPLICATION

### CLINICAL STUDIES

**NDA/Serial Number:** 125261 / 0

**Drug Name:** TRADENAME (ustekinumab) for subcutaneous injection

**Indication(s):** Psoriasis

**Applicant:** Centocor

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**Biometrics Division:** Division of Biometrics III

**Statistics Reviewer:** Kathleen Fritsch, PhD

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**Medical Division:** Division of Dermatology and Dental Products

**Clinical Team:** Brenda Carr, MD / Jill Lindstrom, MD

**Project Manager:** Maria Walsh

**Keywords:** psoriasis, PASI, maintenance dosing

## Table of Contents

<b>1</b>	<b>EXECUTIVE SUMMARY .....</b>	<b>4</b>
1.1	Conclusions and Recommendations .....	4
1.2	Brief Overview of Clinical Studies .....	5
1.3	Statistical Issues and Findings .....	5
<b>2</b>	<b>INTRODUCTION .....</b>	<b>6</b>
2.1	Overview .....	6
2.2	Data Sources .....	8
<b>3</b>	<b>STATISTICAL EVALUATION .....</b>	<b>8</b>
3.1	Evaluation of Efficacy.....	8
3.1.1	Study Design.....	8
3.1.2	Randomization and Blinding .....	10
3.1.3	Week 12 Efficacy Assessment.....	10
3.1.4	Subject Disposition .....	11
3.1.5	Baseline Characteristics .....	13
3.1.6	Week 12 Efficacy Results .....	15
3.1.7	Common Investigators .....	16
3.1.8	Weight-Based Dosing .....	17
3.1.9	PASI 75 versus PGA Success .....	20
3.1.10	Efficacy over Time .....	22
3.2	Evaluation of Safety .....	25
3.2.1	Adverse Events .....	25
<b>4</b>	<b>FINDINGS IN SPECIAL/SUBGROUP POPULATIONS .....</b>	<b>26</b>
4.1	Gender, Race, and Age .....	26
4.2	Other Special/Subgroup Populations .....	28
<b>5</b>	<b>SUMMARY AND CONCLUSIONS .....</b>	<b>31</b>
5.1	Statistical Issues and Collective Evidence.....	31
5.2	Conclusions and Recommendations .....	32

---

<b>6</b>	<b>APPENDIX .....</b>	<b>32</b>
6.1	Biased Coin Randomization Procedure .....	32
6.2	PGA Scale .....	33
6.3	Applicant's Week 12 Disposition Tables.....	34
6.4	Approximate BSA Calculation from PASI Components .....	35
	<b>SIGNATURES/DISTRIBUTION LIST.....</b>	<b>36</b>

## 1 Executive Summary

### 1.1 Conclusions and Recommendations

The efficacy of ustekinumab 45 mg and 90 mg in the treatment of moderate to severe psoriasis has been demonstrated in two clinical studies (Studies 08 and 09). Efficacy at Week 12 was demonstrated through both the protocol-specified primary endpoint of PASI 75 response and the secondary endpoint of PGA response. The PASI 75 response and PGA response results are presented in Table 1.

**Table 1 – Week 12 Efficacy Results**

	Ustekinumab 45 mg	Ustekinumab 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 or 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 or Minimal	278 (68%) p<0.001	302 (73%) p<0.001	20 (5%)

The applicant has proposed that ustekinumab should be dosed initially and 4 weeks later, followed by doses every 12 weeks. In the data submitted by the applicant, subjects in Study 09 were followed through Week 28 (a maximum of 3 doses at Weeks 0, 4, and 16). Subjects in Study 08 were followed through Week 52. After Week 28, subjects received a variable number of doses depending on observed response and randomization assignment. To receive a full year's worth of every 12 week dosing in Study 08, a subject had to maintain PASI 75 response at Weeks 28 and 40 and be randomized to active treatment at Week 40. About 1/3 of the subjects originally randomized to ustekinumab in Study 08 received a full year's worth of every 12 week dosing (77/255 subjects on 45 mg and 85/256 subjects on 90 mg). A comparable proportion were randomized to withdraw treatment at Week 40 (73/255 subjects on 45 mg and 87/256 subjects on 90 mg). The remaining third of subjects were either accelerated to more frequent dosing, terminated for non-response, or dropouts.

The applicant has proposed that subjects weighing 100 kg or less should receive 45 mg at each dosing timepoint and subjects weighing more than 100 kg should receive 90 mg at each dosing timepoint. Although selecting a dose based on weight was not pre-planned by the sponsor, the data do appear to support that weight-based dosing may be appropriate, based on similar efficacy patterns across studies and timepoints. However, the weight-based dosing categories proposed by the sponsor are ad hoc and it is difficult to have any confidence that the sponsor's proposal is in any way an optimal approach.

## 1.2 Brief Overview of Clinical Studies

The applicant has conducted two Phase 3 placebo-controlled studies (08 and 09) to support the safety and efficacy of ustekinumab 45 mg and 90 mg for the treatment of adults with chronic moderate to severe psoriasis who are candidates for phototherapy or systemic therapy. The applicant also conducted a Phase 2 dose-ranging study (Study 04), which is not further discussed in this review. Both studies 08 and 09 are scheduled to follow subjects for 5 years. In this submission, the applicant has submitted data through 52 weeks of follow-up in Study 08 and 28 weeks of follow-up in Study 09. Both studies were conducted in the United States, Canada, and Europe. One-half of the subjects in Study 08 and one-third of the subjects in Study 09 were enrolled in the United States. The timepoint for primary efficacy assessment was Week 12. At Week 12, subjects randomized to placebo were crossed over to active treatment with ustekinumab. The protocol-specified primary efficacy endpoint was PASI 75 response and the first secondary endpoint was a score of clear or minimal on the Physician's Global Assessment. After Week 12, all subjects were treated with ustekinumab. Subjects were treated every 8 weeks or every 12 weeks depending on the PASI response. See Section 3.1.1 for a full description of the study design. Study 08 also included a randomized withdrawal stage where subjects who could maintain response to their assigned dose of ustekinumab were randomized to either continue treatment or withdraw treatment.

**Table 2 – Phase 3 Program for Ustekinumab for Psoriasis**

Study	Treatment Arms	No. of Subjects	Enrollment Period
C0743T08	Ustekinumab 45 mg	255	December 15, 2005 to March 16, 2006
	Ustekinumab 90 mg	256	
	Placebo to Ustekinumab 45 mg	127	
	Placebo to Ustekinumab 90 mg	128	
C0743T09	Ustekinumab 45 mg	409	March 20, 2006 to September 5, 2006
	Ustekinumab 90 mg	411	
	Placebo to Ustekinumab 45 mg	205	
	Placebo to Ustekinumab 90 mg	205	

## 1.3 Statistical Issues and Findings

The clinical studies demonstrated that ustekinumab is efficacious relative to placebo in the treatment of psoriasis. Both studies demonstrated statistical significance for the primary and secondary efficacy endpoints at Week 12. Results were consistent across studies and endpoints. The amount of missing data was relatively small (<4%) at Week 12. Both the 45 mg and the 90 mg dose of ustekinumab had very similar response rates. Although the studies evaluated fixed dosing irrespective of weight, the applicant has proposed that the recommended dosing regimen would be for subjects  $\leq 100$  kg to use 45 mg and subjects  $> 100$  kg to use 90 mg. Analyses at multiple timepoints and across multiple endpoints in both studies support the assertion selecting a dose based on weight could help maximize efficacy while minimizing total exposure to ustekinumab. Both the 45 mg and 90 mg doses are effective across the full range of subject weights. The weight group with the lowest response rate—subjects weighing over 130 kg—had PASI 75 response rates of at least 40% on ustekinumab. Thus it appears that any recommended

dosing regimen based on weight using doses in the range of 45 to 90 mg would be an effective regimen. However, it appears that much is still not known about how to optimize dose based on weight.

Typically the Division recommends using separate sets of investigators for each pivotal Phase 3 study so that the studies are independent. Studies 08 and 09 had a number of investigators who participated in both studies. Response rates for subjects with investigators who participated in both studies were slightly higher than for those where the investigator participated in only one study. However, these differences were not large, and because of the magnitude of the treatment effect for ustekinumab, efficacy claims are still supported even when only subjects from unique investigators are considered.

Efficacy was generally consistent across most demographic subsets, such as gender and country. The studies enrolled too few non-Caucasians subjects and subjects age 65 and older to compare efficacy across race and age groups. Ustekinumab was effective across the range of baseline severity from moderate to severe.

## **2 Introduction**

### **2.1 Overview**

Ustekinumab for subcutaneous injection is an IL-12 and 23 antagonist intended for the treatment of chronic moderate to severe psoriasis. The molecule is a first-in-class new molecular entity. The safety and efficacy of ustekinumab are primarily supported by two Phase 3 studies, C0743T08 and C0743T09. The sponsor's development program also included a Phase 2 dose-ranging study (C0379T04).

The Phase 3 protocols were designed during a period of reorganization at the Agency in which responsibility for therapeutic biologic products was dispersed from one office dedicated to the review of biologic products (ODE VI) to multiple divisions responsible for both drug and biologic products. The general designs of the Phase 3 studies were discussed with ODE VI at an End of Phase 2 Meeting on May 26, 2005, and features such as the primary efficacy endpoint were agreed upon with ODE VI. The responsibility for the IND for ustekinumab for psoriasis was transferred to the Division of Dermatology and Dental Products with the Center reorganization in October 2005. Protocols 08 and 09 were submitted to the Agency in around this time in September and December 2005, respectively.

The two Phase 3 studies are the primary focus of this review. The Phase 3 studies evaluated two dose concentrations (45 mg and 90 mg) versus placebo. Studies 08 and 09 are both 5-year studies with several stages and pre-planned database locks. After an initial 12-week placebo controlled period, all subjects received treatment with ustekinumab on various schedules depending on the subject's response at various key timepoints. The applicant submitted data from Study 08 through Week 52 and from Study 09 through Week 28.

The studies enrolled subjects 18 years of age and older who had had plaque-type psoriasis for 6 months or more. Subjects were to have baseline PASI (Psoriasis Area and Severity Index) score  $\geq 12$ , were to have psoriasis covering  $\geq 10\%$  total body surface area, and were to be candidates for phototherapy or systemic therapy. Study 08 enrolled 766 subjects and Study 09 enrolled 1230 subjects. At the beginning of the study, subjects were randomized 1:1:1 to 45 mg, 90 mg, or placebo. Study 08 randomized 255 subjects to 45 mg, 256 subjects to 90 mg, and 255 subjects to placebo. Study 09 randomized 409 subjects to 45 mg, 411 subjects to 90 mg, and 410 subjects to placebo. The studies were conducted in the United States, Canada, and Europe (Austria, Belgium, France, Germany, Switzerland, and UK). The numbers of subjects and centers by country are presented in Table 3.

**Table 3 – Number of Centers and Subjects per Country**

Study 08 (N=766)		Study 09 (N=1230)			
# Centers	# Subjects	# Centers	# Subjects	# Centers	# Subjects
US (28)	382 (50%)	US (32)	415 (34%)	Germany (10)	149 (12%)
Canada (16)	371 (48%)	Canada (19)	599 (49%)	Switzerland (2)	11 (1%)
Belgium (3)	13 (2%)	Austria (3)	18 (1%)	UK (3)	6 (<1%)
		France (1)	31 (3%)		

The enrollment period for Study 08 ran from December 15, 2005 to March 16, 2006. The first subjects enrolled in Study 09 were entered after enrollment from Study 08 was complete, and the enrollment period for Study 09 ran from March 20, 2006 to September 5, 2006. Several investigators were involved in both studies. As the enrollment periods for the two studies did not overlap, the investigators who participated in both studies enrolled subjects first into Study 08 and later into Study 09. Six US investigators and 13 Canadian investigators participated in both studies. The 6 US investigators enrolled 124 (16%) subjects in Study 08 and 164 (13%) subjects in Study 09. The 13 Canadian investigators enrolled 308 (40%) subjects in Study 08 and 458 (37%) subjects in Study 09. Thus, the investigators who participated in both studies enrolled approximately half of the subjects in each study.

The primary efficacy assessment timepoint was Week 12. The primary efficacy endpoint was PASI 75 (75% or greater reduction in PASI score). The major secondary efficacy endpoints were the proportion of subjects with a Physician's Global Assessment (PGA) score of cleared or minimal at Week 12, change in Dermatology Life Quality Index (DLQI) at Week 12, and (for Study 08 only) time to loss of PASI 75 response for subjects randomized to withdraw treatment versus those randomized to continue treatment.

The sponsor has proposed the following dosing regimen for ustekinumab. The initial dose should be followed by a second dose 4 weeks later, subsequent doses should follow every 12 weeks thereafter. The sponsor has proposed that patients weighing less than or equal to 100 kg should receive doses of 45 mg and patients greater than 100 kg should receive doses of 90 mg. In the clinical studies, subjects were randomly assigned to either 45 mg or 90 mg arms regardless of weight (weight was a stratification factor, however).

## 2.2 Data Sources

This reviewer evaluated the sponsor's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in eCTD format and was entirely electronic. The datasets used in this review are archived at \\Cbsap58\M\ eCTD\_Submissions\0000\m5\datasets.

## 3 Statistical Evaluation

### 3.1 Evaluation of Efficacy

#### 3.1.1 Study Design

Studies C0743T08 and C0743T09 were randomized, double-blind studies of 45 mg and 90 mg ustekinumab and placebo in the treatment of psoriasis. Both studies have several stages. The two studies had identical designs through Week 28, but had different designs from Weeks 28 to 52. The initial randomization determined the treatment schedule for the first 28 weeks. Subjects were randomized to receive an initial treatment cycle of 45 mg, 90 mg, or placebo at Weeks 0 and 4. The primary timepoint for efficacy evaluation was Week 12. At Week 12, subjects randomized to placebo were crossed over to active treatment and received doses of 45 mg or 90 mg at Weeks 12 and 16. Subjects originally randomized to active treatment received a maintenance dose at Week 16. Thus, the initial randomization consisted of four treatment groups in Studies 08 and 09:

1. 45 mg ustekinumab at Weeks 0, 4, and 16
2. 90 mg ustekinumab at Weeks 0, 4, and 16
- 3a. placebo at Weeks 0 and 4, 45 mg ustekinumab at Weeks 12 and 16
- 3b. placebo at Weeks 0 and 4, 90 mg ustekinumab at Weeks 12 and 16

Both studies had the same general premise for selecting maintenance dosing regimens in the later stages of the study: responding subjects were to continue every 12 week dosing, and partial responders were to accelerate to every 8 week dosing. However, each study also included one randomized component in the maintenance stages and also had an escape mechanism for non-responding subjects at Week 28. In Study 08, subjects who had demonstrated that they could maintain response at key timepoints with every 12 week dosing were randomized to withdraw treatment or continue every 12 week dosing at Week 40. In Study 09, subjects who were partial responders were randomized to either continue every 12 week dosing or switch to every 8 week dosing.

Specifically, the study design in Study 08 for Week 28 to Week 52 is as follows. Subjects were assigned to additional maintenance doses at Week 28 based on their Week 28 PASI response. At Week 28, subjects who were

- *Nonresponders* (<50% improvement in PASI score from baseline to Week 28) were discontinued with no further dosing
- *Partial Responders* ( $\geq 50\%$  to <75% improvement in PASI from baseline to Week 28) were assigned to every 8 week dosing through Week 52 (dosing at Weeks 28, 36, and 44) with the original concentration (45 mg or 90 mg)

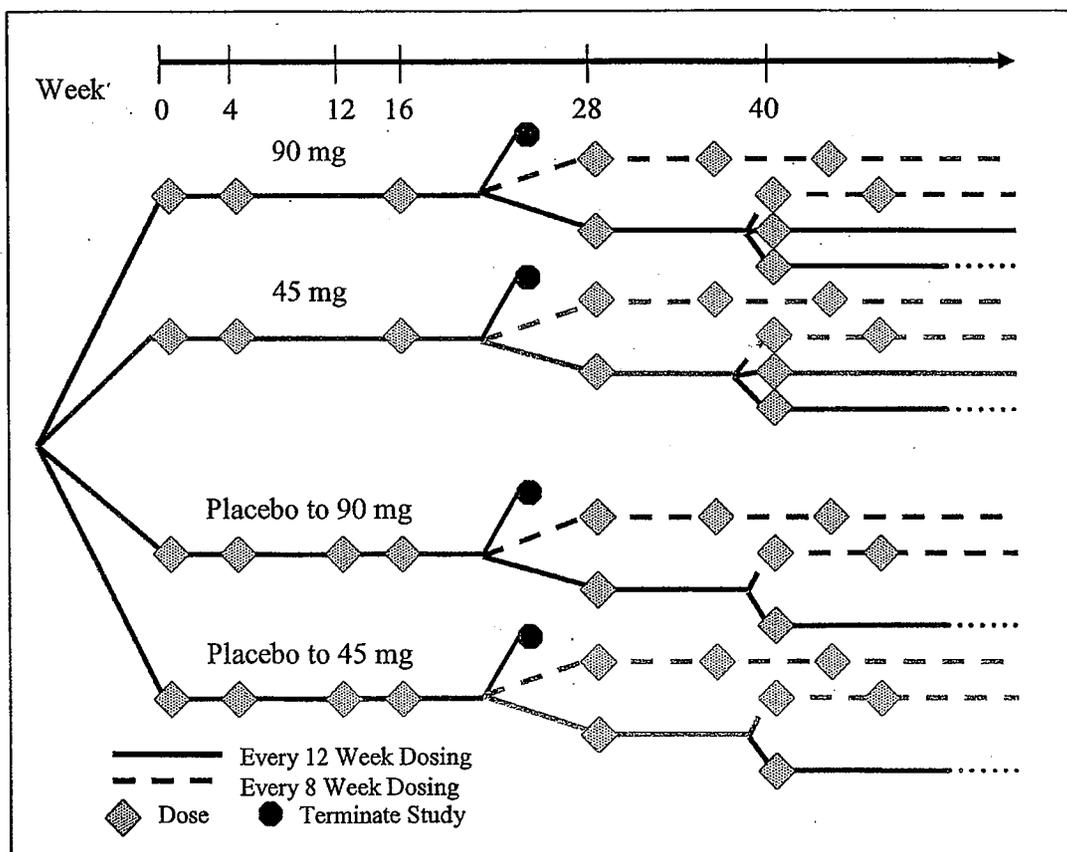
- *Responders* ( $\geq 75\%$  improvement in PASI from baseline to Week 28) were assigned to continue every 12 week dosing (dosing at Week 28) with the same concentration (45 mg or 90 mg) with re-assessment at Week 40

Subjects who were Responders at Week 28 were re-assessed at Week 40. Subjects who were Responders at Week 28 and who at Week 40 were

- *Responders* and originally randomized to *active* treatment (groups 1 and 2) were randomized (1:1) to either continue every 12 week dosing (dose at Week 40) or withdraw treatment (placebo at Week 40).
- *Responders* and originally randomized to *placebo* (groups 3a and 3b) were assigned to withdraw treatment (placebo at Week 40).
- *Partial or Nonresponders* were assigned to every 8 week dosing (dosing at Weeks 40 and 48) at the original concentration.

Subjects who were randomized to withdraw treatment at Week 40 were to re-initiate dosing at the visit where they dropped below 50% of their Week 40 PASI percent improvement. For example, a subject with a PASI percent improvement of 80% from baseline to Week 40 would re-initiate treatment at the visit where their PASI percent improvement dropped below 40%. A schematic for the study design in Study 08 is presented in Figure 1. The sponsor has submitted data through Week 52 for Study 08.

Figure 1 – Study Design Schematic for Study 08



For Study 09, the sponsor has submitted data only through Week 28. However, the design of Study 09 from Week 28 to Week 52 is briefly described below to contrast with Study 08. In Study 09, subjects at Week 28 who are

- *Nonresponders* were to be discontinued with no further dosing
- *Partial Responders* and originally randomized to *active* treatment (groups 1 and 2) were to be randomized to either every 8 week dosing or every 12 week dosing
- *Partial Responders* and originally randomized to *placebo* treatment (groups 3a and 3b) were assigned to every 8 week dosing
- *Responders* were assigned to continue every 12 week dosing with re-assessment at Week 40. At Week 40, subjects who became Partial or Non-responders were to begin every 8 week dosing.

### 3.1.2 Randomization and Blinding

To maintain blinding all subjects received the same number of injections. Because a 90 mg dose has double the volume of the 45 mg dose (1 mL vs. 0.5 mL) all subjects received a 0.5 mL injection and a 1 mL injection at each visit where any subjects were scheduled to receive active doses (Weeks 0, 4, 12, 16, 28, 36, 40, 44, 48, and 52). Subjects assigned to a 45 mg dose received 45 mg of ustekinumab at 1 mL of placebo (the vehicle). Similarly subjects assigned to a 90 mg dose received 90 mg of ustekinumab and 0.5 mL of placebo. Subjects assigned to placebo received two placebo injections. To maintain the blind investigators used the IVRS (interactive voice response system) to identify study agent for administration.

Randomization was stratified on three variables – center, weight ( $\leq 90$  kg or  $> 90$  kg), and previous experience with systemic therapies for psoriasis (inadequate response or contraindication to  $< 3$  or  $\geq 3$  therapies). Subjects were randomized using an adaptive randomization method using minimization with biased-coin assignment. The details of this randomization procedure are given in Appendix 6.1.

### 3.1.3 Week 12 Efficacy Assessment

The primary efficacy endpoint was PASI 75 (at least 75% improvement in PASI score from baseline) at Week 12. The first major secondary endpoint was a score of clear or minimal on the PGA at Week 12. The definition of the PGA scale can be found in Appendix 6.2. Both endpoints were to be analyzed with a Cochran-Mantel-Haenszel test stratified on pooled site and weight ( $\leq 90$  kg or  $> 90$  kg). Multiplicity due to two doses being evaluated was controlled using Holm's method (smaller p-value compared with 0.025 and larger p-value compared with 0.05 if the first test is significant).

The ITT population was defined as all randomized subjects. Subjects who discontinued study treatment due to unsatisfactory therapeutic effect or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis were considered treatment failures. Subjects with missing PASI or PGA scores at Week 12 were considered failures.

The per protocol (PP) population excluded subjects who did not meet certain inclusion and exclusion criteria: BSA  $\geq$  10% or PASI  $\geq$  12 at baseline, had non-plaque psoriasis (erythrodermic, guttate, or pustular), had previously used a therapeutic agent targeting IL-12 or IL-23, or were participating in another clinical trial. The PP population also excluded subjects who did not receive full and correct injections at Weeks 0 and 4.

### 3.1.4 Subject Disposition

For the purposes of this review, the 'Week 12 Disposition' accounts for subjects who were not directly evaluable for efficacy at the Week 12 visit. This includes subjects missing efficacy data at Week 12 as well as subjects classified per the protocol as treatment failures prior to Week 12. The protocol classified subjects who discontinued study treatment due to unsatisfactory therapeutic effect or an AE of worsening of psoriasis, or who started a protocol-prohibited medication/therapy during the study that could improve psoriasis as treatment failures in Week 12 analyses.

The applicant's study reports use a slightly broader definition for the Week 12 disposition, tracking all subjects discontinuing treatment by Week 12. This essentially includes all subjects who did not receive the scheduled treatment at Week 12. The applicant's definition includes additional subjects who attended the Week 12 visit and were evaluable for efficacy, but did not receive an injection at Week 12. For completeness, the applicant's tables are included in Appendix 6.3.

Study 08 randomized 766 subjects (255 to 45 mg ustekinumab, 256 to 90 mg ustekinumab, and 255 to placebo). One subject (randomized to 90 mg ustekinumab) was randomized in error, and never received any treatments. The remaining 765 subjects received the initial Week 0 randomized treatment. At Week 4, all 255 (100%) of subjects randomized to 45 mg ustekinumab received the Week 4 dose, 251/256 (98%) of subjects randomized to 90 mg ustekinumab received the Week 4 dose, and 250/255 (98%) of subjects randomized to placebo received the Week 4 dose. The reasons for which the 90 mg subjects did not receive the Week 4 treatment included: randomized in error/never treated (1), adverse event (2), failure to fulfill exclusion criteria (1) and subject moved (1). The reasons for which the placebo subjects did not receive the Week 4 treatment included: adverse event (3), unsatisfactory therapeutic effect (1), and subject withdrew consent (1).

In total, 18 subjects (1 (<1%) ustekinumab 45 mg, 7 (3%) ustekinumab 90 mg, and 10 (4%) placebo subjects) were not evaluable for efficacy at Week 12, either because the subject had missing Week 12 data, or because the subject was previously classified as a treatment failure. See Table 4. Adverse events were the most common reason for discontinuing treatment in the placebo arm, but no pattern is observed in the ustekinumab-treated subjects, except that more 90 mg than 45 mg subjects discontinued.

**Table 4 – Week 12 Disposition (Study 08)**

	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
Subjects Randomized	255	256	255
Subjects Receiving Week 0 Dose	255	255	255
Subjects Receiving Week 4 Dose	255 (100%)	251 (98%)	250 (98%)
Subjects Not Evaluable at Week 12	1 (<1%)	7 (3%)	10 (4%)
Classified as Treatment Failure	1	2	8
Missing	-	5	2
<b>Discontinuation Reason</b>			
Never Treated	-	1	-
Adverse Event	-	2	5
Unsatisfactory Therapeutic Effect	-	1	3
Lost to Follow-Up	-	1	1
Other			
Prohibited Medication Use	1	-	-
Inclusion/Exclusion Criteria	-	1	-
Subject Request	-	1	1

Study 09 randomized 1230 subjects (409 to 45 mg ustekinumab, 411 to 90 mg ustekinumab, and 410 to placebo). All 1230 subjects received the initial Week 0 randomized treatment. At Week 4, 406/409 (99%) of subjects randomized to 45 mg ustekinumab received the Week 4 dose, 409/411 (99%) of subjects randomized to 90 mg ustekinumab received the Week 4 dose, and 400/410 (98%) of subjects randomized to placebo received the Week 4 dose. The reasons for which the 45 mg subjects did not receive the Week 4 treatment included: lost to follow-up (2), and prohibited concomitant medication (1). The reasons for which the 90 mg subjects did not receive the Week 4 treatment included: lost to follow-up (1), and failure to fulfill exclusion criteria (1). The reasons for which the placebo subjects did not receive the Week 4 treatment included: adverse event (6), unsatisfactory therapeutic effect (2), subject withdrew consent (1), and failure to fulfill inclusion criteria (1).

In total, 18 subjects (4 (1%) ustekinumab 45 mg, 4 (1%) ustekinumab 90 mg, and 14 (3%) placebo subjects) were not evaluable for efficacy at Week 12, either because the subject had missing data at the Week 12 visit, or because the subject was previously classified as a treatment failure. See Table 5. Again, adverse events were the most common reason for discontinuation for placebo subjects. For ustekinumab-treated subjects, lost to follow-up was the most common reason. The 45 mg and 90 mg groups had similar numbers of dropouts.

**Table 5 – Week 12 Disposition (Study 09)**

	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
Subjects Randomized	409	411	410
Subjects Receiving Week 0 Dose	409	411	410
Subjects Receiving Week 4 Dose	406	409	400
Subjects Not Evaluable at Week 12	4 (1%)	4 (1%)	14 (3%)
Classified as Treatment Failure	-	-	9
Missing	4	4	5
Reason Not Observable at Week 12			
Adverse Event	1	1	7
Unsatisfactory Therapeutic Effect	-	-	2
Lost to Follow-Up	3	1 <sup>a</sup>	2
Death	-	1	-
Other			
Prohibited Medication Use	-	-	-
Inclusion/Exclusion Criteria	-	1	1
Subject Request	-	-	2

<sup>a</sup> Reason marked as 'Other' with description 'Lost to Follow-up'

### 3.1.5 Baseline Characteristics

Baseline demographics were generally balanced across treatment groups in Studies 08 and 09. Approximately 2/3 of the subjects were male and 1/3 female in both studies. More than 90% of the subjects were Caucasian. The mean age was around 45 and the mean weight was 94 kg in Study 08 and 91 kg in Study 09. About 1/2 of the subjects in Study 08 were from the U.S., as were about 1/3 of the subjects in Study 09. About 1/2 of the subjects in each study were from Canada, and the rest were from Europe (2% in Study 08 and 18% in Study 09). See Table 6 and Table 7.

**Table 6 – Baseline Demographics (Study 08)**

	Ustekinumab 45 mg N=255	Ustekinumab 90 mg N=256	Placebo N=255
<i>Age (years)</i>			
Mean	44.8	46.2	44.8
Range	19 – 69	19 -76	19 – 74
<i>Gender</i>			
Male	175 (69%)	173 (68%)	183 (72%)
Female	80 (31%)	83 (32%)	72 (28%)
<i>Race</i>			
Caucasian	245 (96%)	237 (93%)	235 (92%)
Black	4 (2%)	6 (2%)	4 (2%)
Asian	2 (1%)	6 (2%)	12 (5%)
Other	4 (2%)	7 (3%)	4 (2%)

<Table Continues on Next Page>

**Table 6 <Continued>- Baseline Demographics (Study 08)**

	Ustekinumab 45 mg N=255	Ustekinumab 90 mg N=256	Placebo N=255
<i>Weight (kg)</i>			
Mean (SD)	93.7 (23.8)	93.8 (23.9)	94.2 (23.5)
Range	48 – 165	47 – 183	47 – 158
<i>Country/Region</i>			
United States	126 (49%)	126 (49%)	130 (51%)
Canada	124 (49%)	125 (49%)	122 (48%)
Europe	5 (2%)	5 (2%)	3 (1%)

**Table 7 – Baseline Demographics (Study 09)**

	Ustekinumab 45 mg N=409	Ustekinumab 90 mg N=411	Placebo N=410
<i>Age (years)</i>			
Mean	45.1	46.6	47.0
Range	18 - 77	18 - 77	18 - 86
<i>Gender</i>			
Male	283 (69%)	274 (67%)	283 (69%)
Female	126 (31%)	137 (33%)	127 (31%)
<i>Race</i>			
Caucasian	372 (91%)	375 (91%)	381 (93%)
Black	10 (2%)	8 (2%)	9 (2%)
Asian	16 (4%)	19 (5%)	15 (4%)
Other	11 (3%)	9 (2%)	5 (1%)
<i>Weight (kg)</i>			
Mean (SD)	90.3 (21.0)	91.5 (21.3)	91.1 (21.6)
Range	45 - 195	37 - 171	47 - 185
<i>Country/Region</i>			
United States	135 (33%)	140 (34%)	141 (34%)
Canada	200 (49%)	203 (49%)	196 (48%)
Europe	74 (18%)	68 (17%)	73 (18%)

Subjects were required to have a baseline body surface area (BSA) involvement of at least 10%. Subjects averaged about 26% involvement, and had mean PASI scores of about 20 (the minimum for inclusion was a PASI score of 12. Specific PGA scores were not required, and about 55-60% of subjects had mild or moderate scores on the PGA while 40-45% of subjects had marked or severe scores. See Table 8 and Table 9.

**Table 8 – Baseline Disease Characteristics (Study 08)**

	Ustekinumab 45 mg N=255	Ustekinumab 90 mg N=256	Placebo N=255
<i>BSA (%)</i>			
Mean (SD)	27.2 (17.5)	25.2 (15.0)	27.7 (17.4)
Range	10 - 96	10 - 82	10 - 88
<i>PASI</i>			
Mean (SD)	20.5 (8.6)	19.8 (7.6)	20.4 (8.6)
Range	12 - 62	12 - 56	12 - 62
<i>PGA</i>			
Mild	17 (7%)	13 (5%)	12 (5%)
Moderate	124 (49%)	133 (52%)	131 (51%)
Marked	100 (39%)	96 (38%)	102 (40%)
Severe	14 (6%)	13 (5%)	10 (4%)

**Table 9 – Baseline Disease Characteristics (Study 09)**

	Ustekinumab 45 mg N=409	Ustekinumab 90 mg N=411	Placebo N=410
<i>BSA (%)</i>			
Mean (SD)	25.9 (15.5)	27.1 (17.4)	26.1 (17.4)
Range	10 - 88	10 - 96	10 - 98
<i>PASI</i>			
Mean (SD)	19.4 (6.8)	20.1 (7.5)	19.4 (7.5)
Range	12 - 47	12 - 49	12 - 61
<i>PGA</i>			
Mild	31 (8%)	27 (7%)	38 (9%)
Moderate	209 (51%)	225 (55%)	212 (52%)
Marked	148 (36%)	137 (33%)	139 (34%)
Severe	21 (5%)	22 (5%)	21 (5%)

**3.1.6 Week 12 Efficacy Results**

Both ustekinumab 45 mg and 90 mg were superior to placebo at Week 12 for the primary endpoint of PASI 75 response and the secondary endpoint of PGA response in both studies. The results are statistically significant when the multiplicity adjustment for two dose levels is taken into account (Holm's method). The ITT and per protocol results are very similar and are presented in Table 10 and Table 11.

**Table 10 – 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 11 – 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%)

### 3.1.7 Common Investigators

Study 08 enrolled 766 subjects at 47 centers, while Study 09 enrolled 1230 subjects at 70 centers. The maximum center enrollment in Study 08 was 39 subjects and the maximum center enrollment in Study 09 was 53 subjects. With the large number of centers and relatively small sample sizes, the impact of any individual center on the efficacy results is limited. However, 6 US investigators and 13 Canadian investigators participated in both studies. The 6 US investigators enrolled 124 (16%) subjects in Study 08 and 164 (13%) subjects in Study 09. The 13 Canadian investigators enrolled 308 (40%) subjects in Study 08 and 458 (37%) subjects in Study 09. Thus, the investigators who participated in both studies enrolled approximately half of the subjects in each study.

The groups of common and unique investigators had similar efficacy in Study 08, however, the group of common investigators showed greater efficacy for the 90 mg dose in Study 09. Efficacy results by whether the investigator participated in both Studies 08 and 09 or only one study are presented in Table 12 and Table 13. Even if only the

subjects from the investigators who participated in just one study are considered, both ustekinumab 45 mg and 90 mg are superior to placebo ( $p < 0.001$ ).

**Table 12 – Week 12 PASI 75 Results by Common versus Unique Investigators (Study 08)**

Investigator Participated in:	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
Both Studies	101/146 (69%)	98/143 (69%)	5/143 (3%)
Study 08 Only	70/109 (64%)	72/113 (64%)	3/112 (3%)

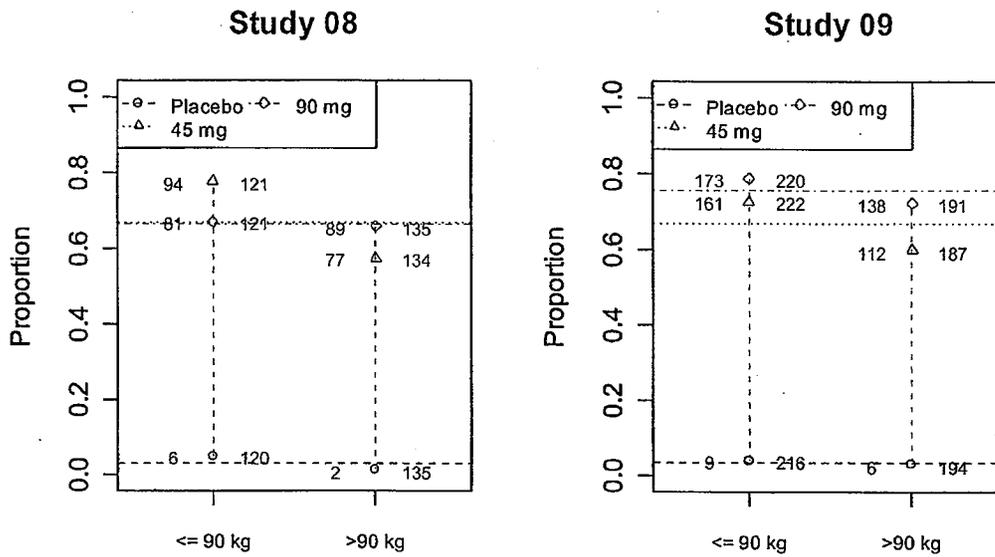
**Table 13 – Week 12 PASI 75 Results by Common versus Unique Investigators (Study 09)**

Investigator Participated in:	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
Both Studies	144/209 (69%)	175/208 (84%)	8/205 (4%)
Study 09 Only	129/200 (65%)	136/203 (67%)	7/205 (3%)

### 3.1.8 Weight-Based Dosing

The protocols proposed three weight subgroup analyses of the primary endpoint: by weight strata ( $\leq 90$  kg,  $> 90$  kg), by weight quartiles, and by 10 kg weight increments. Graphs for the PASI 75 response rates by weight strata at Week 12 are presented in Figure 2, and graphs for the PASI 75 response rates at Week 12 by 10 kg weight increments are presented in Figure 3 and Figure 4. The general pattern observed in the plots is that the response rate decreases as weight increases, and that the response rate decreases faster in the 45 mg arm. Similar patterns are observed at other timepoints, such as Week 28.

**Figure 2 – PASI 75 Response Rates at Week 12 by Weight Strata**



Note: Numbers represent the number of success (on the left) and the number of subjects (on the right) per subgroup.

**Figure 3 – PASI 75 Response Rates at Week 12 by 10 kg Weight Groups (Study 08)**

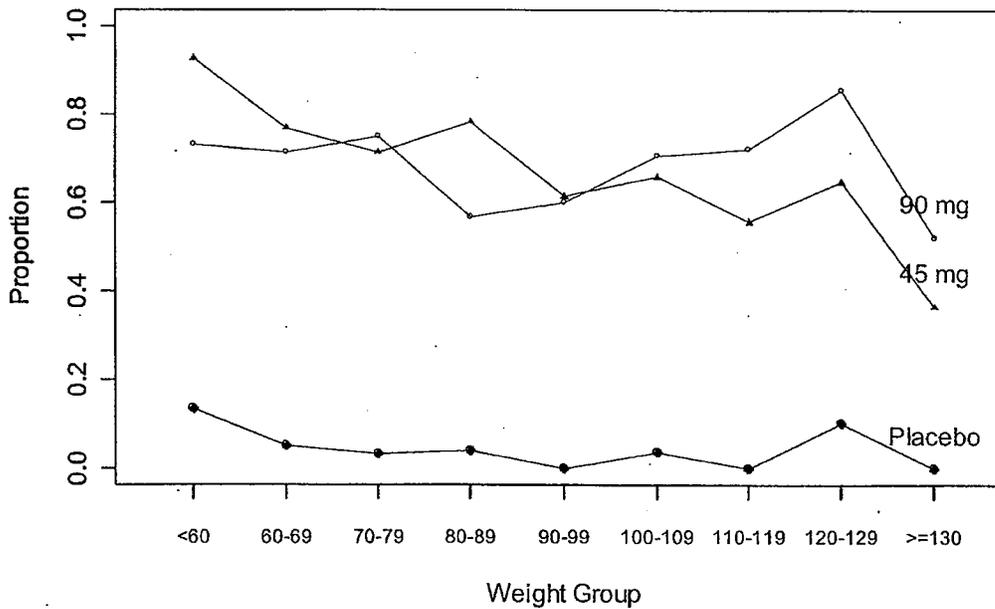
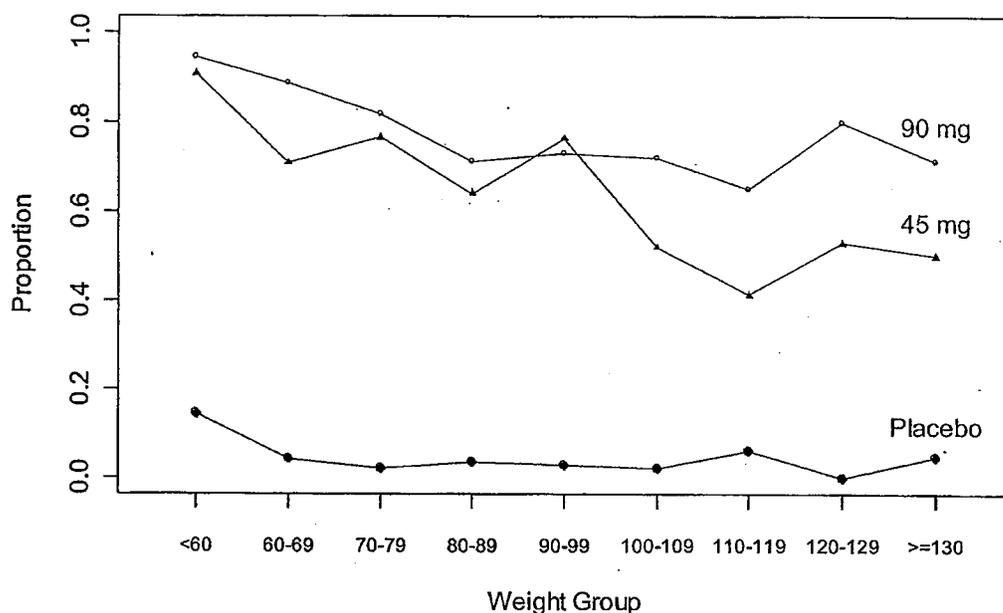


Figure 4 - PASI 75 Response Rates at Week 12 by 10 kg Weight Groups (Study 09)



Based in part by this type of graphical presentation (pharmacokinetic modeling also supports that weight may be an important factor in determining drug blood levels and response), the sponsor has proposed that the appropriate dose for marketing is for patients up to 100 kg to receive 45 mg at each scheduled dose and for patients over 100 kg to receive 90 mg at each scheduled dose. The sponsor's decision to determine dosing based on two weight groups is ad hoc. One concern with selecting a dose based on observed subgroup results is that any conclusions based on the examination of many subgroups could be due to chance.

The general pattern that response decreases as subject weight increases is observed in both clinical trials, is observed both on subjects originally randomized to ustekinumab as well as those crossed over to ustekinumab at Week 12 (data not shown), as well as is supported by pharmacokinetic data (not discussed in this review—refer to the pharmacometrician's review.) This pattern is also observed at multiple timepoints. Thus, although evaluating weight-based dosing was not an objective of these trials, the preponderance of observation data appears to support that the optimal dose to maximize efficacy may depend on a subject's weight. In addition, because both doses were superior to placebo across the full range of weights, any weight-based dosing scheme within the range of doses studied would be effective for a population comparable to the one studied in the clinical trials. However, beyond this, it is not possible with any level of confidence to determine based on an examination of subgroups which dose is optimal for subjects of a certain weight. Thus in summary, while it appears that the studies provide sufficient information to determine that the sponsor's proposed regimen (45 mg for patients  $\leq 100$  kg and 90 mg for patients  $> 100$  kg) is an effective dose for the study

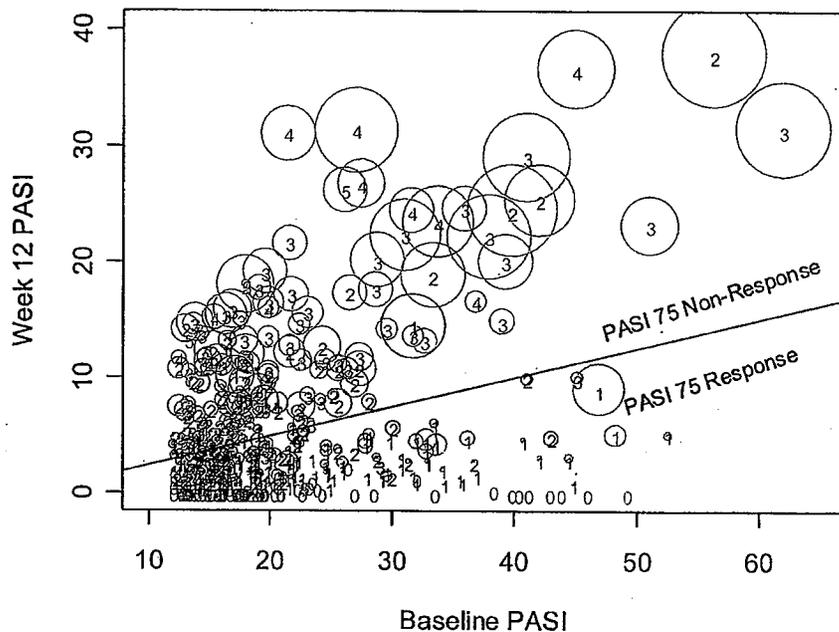
population comparable to the studied population, it is not possible to provide any level of confidence that the proposed regimen is a truly optimal one.

### 3.1.9 PASI 75 versus PGA Success

The Week 12 PASI 75 response rates and the Week 12 PGA response rates are similar, with slightly higher response rates from PASI 75 than from PGA success. The following figures (Figure 5 and Figure 6) were created to explore the characteristics of subjects who were responders under both endpoints as well as those subjects who were responders under only one of the endpoints. The figures display the Week 12 PASI versus the Baseline PASI for subjects receiving either dose of ustekinumab. PASI 75 responders are represented by points below the line. The Week 12 PGA scores (0 to 5) are used as the plotting symbols. Thus, the orange and blue points represent subjects who were PASI 75 responders. Orange and pink points represent subjects who were PGA responders. The diameters of the circles around each point are proportional to the approximate BSA at Week 12. Symbols without visible circles had small BSAs (<3%). Note, the BSA was not recorded at Week 12, but this reviewer used the surface area component of the PASI scale to calculate an approximate Week 12 BSA. See Appendix 6.4 for a description of how the BSA was approximated.

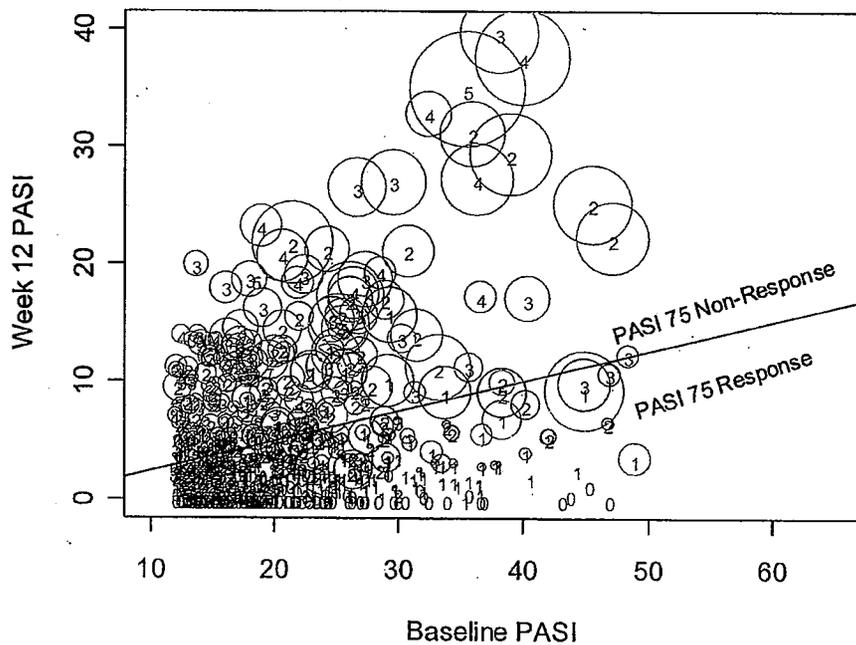
The figures give us some insight into why subjects may have been classified as responders under one endpoint but not the other. BSA appears to be an important factor among many subjects who were responders under only one endpoint. Some subjects who were PGA responders but not PASI 75 responders (points above the line with symbol '1' [represented in pink]), were subjects with disease of minimal severity, but larger BSA involvement (points surrounded by large circles). It is more difficult to decipher any patterns among the subjects who were PASI 75 responders but not PGA responders (points below the line with symbols '2' or '3' [represented in blue]). However, many of these subjects appear to have relatively small BSAs (small circles).

**Figure 5 – Week 12 PASI versus Baseline PASI with Week 12 PGA and BSA (Study 08 – Subjects Treated with Ustekinumab 45 mg or 90 mg)**



Note: Symbols = Week 12 PGA. Circle diameters are proportional to the Week 12 BSA.

**Figure 6 – Week 12 PASI versus Baseline PASI with Week 12 PGA and BSA (Study 09 – Subjects Treated with Ustekinumab 45 mg or 90 mg)**



Note: Symbols = Week 12 PGA. Circle diameters are proportional to the Week 12 BSA.

### 3.1.10 Efficacy over Time

Studies 08 and 09 were designed to follow all subjects through Week 28 with dosing determined by the initial randomization. Subjects were evaluated for PASI and PGA every 4 weeks (plus Week 2) during this interval. Subjects initially randomized to ustekinumab received doses at Weeks 0, 4, and 16. Subjects initially randomized to placebo received placebo at Weeks 0 and 4 and ustekinumab 45 mg or 90 mg at Weeks 12 and 16. The PASI 75 response rates through Week 28 are presented in Figure 7 and Figure 8. The graphs for the PGA response rates are similar (not shown). Efficacy generally plateaued after Week 12 for subjects on ustekinumab, though the response rate did increase slightly following the Week 16 dose. Subjects originally randomized to placebo followed a similar pattern after switching to ustekinumab and achieved similar response rates.

Figure 7 – PASI 75 Response Rates through Week 28 (Study 08)

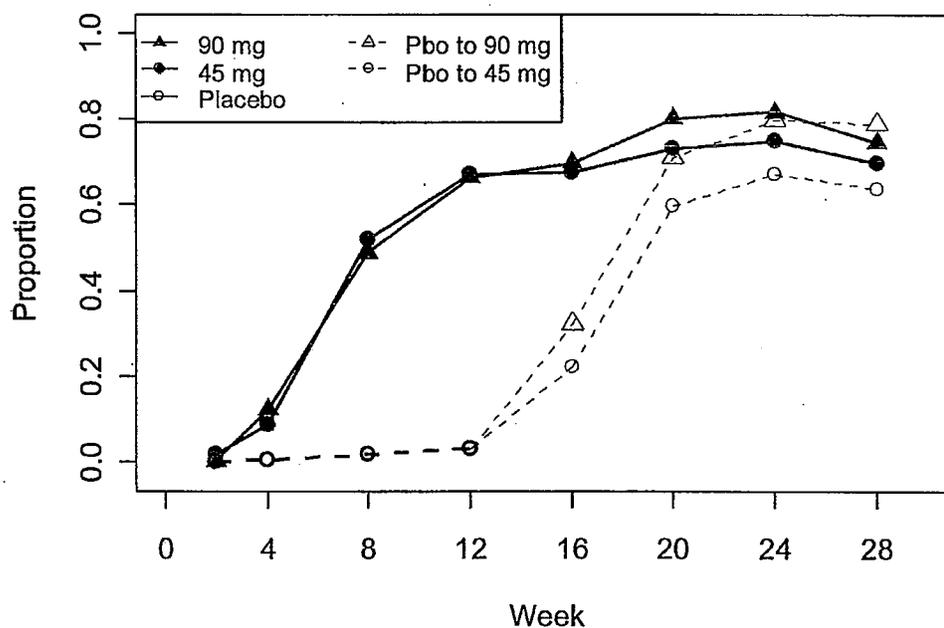
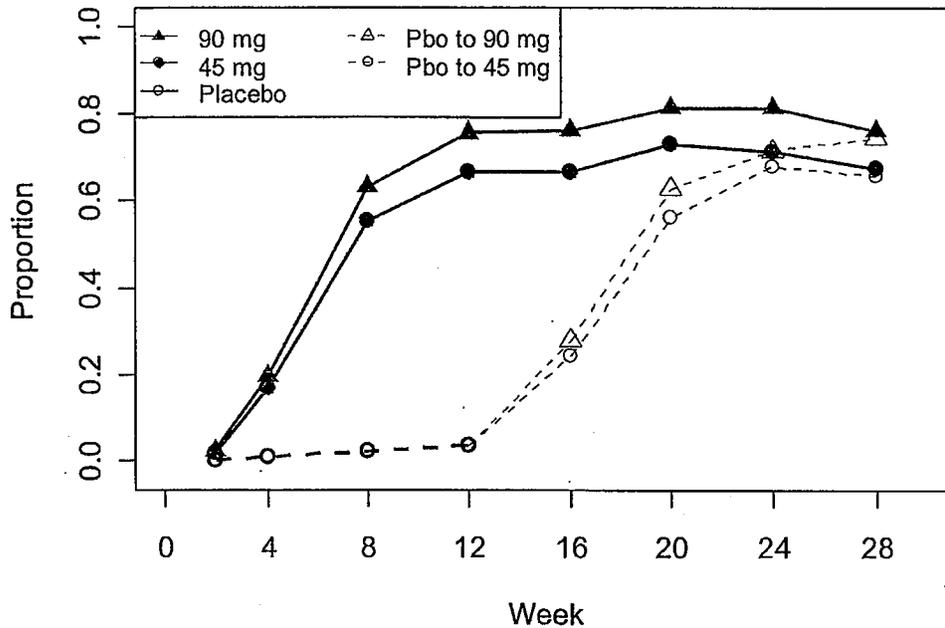


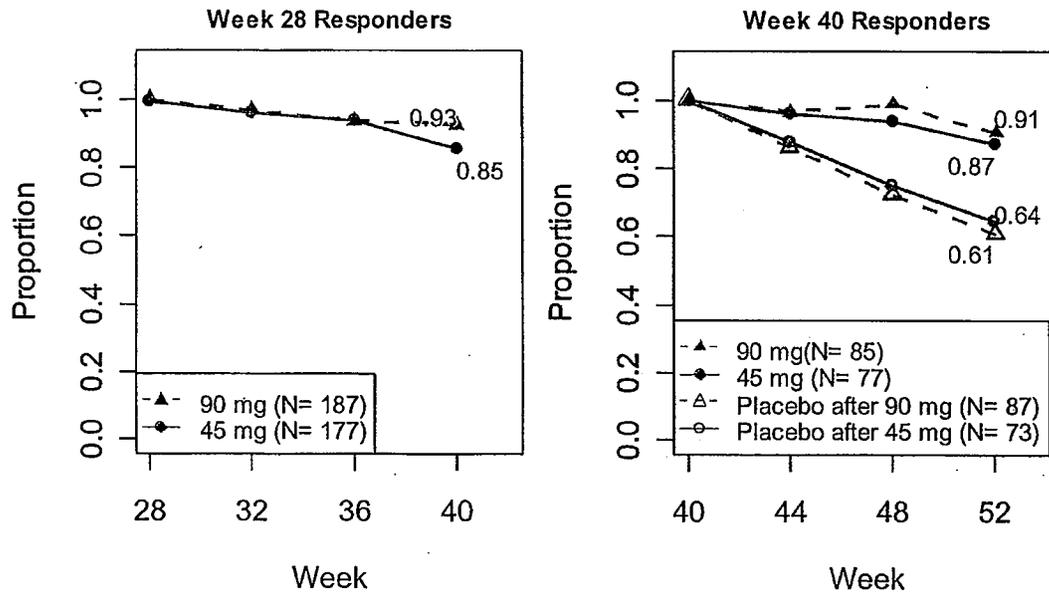
Figure 8 – PASI 75 Response Rates through Week 28 (Study 09)



After Week 28, the dosing schedule in Study 08 depended on subject response. Among the 255 subjects randomized to 45 mg of ustekinumab, at Week 28, 177 (69%) were PASI 75 responders and were assigned to continue every 12 week dosing, 49 (19%) were partial responders (50 to 75% improvement in PASI) and were accelerated to every 8 week dosing, and 17 (7%) subjects were terminated from treatment for non-response (< 50% improvement in PASI). Among the 256 subjects randomized to 90 mg of ustekinumab, at Week 28, 187 (73%) were PASI 75 responders and were assigned to continue every 12 week dosing, 44 (17%) were partial responders and were accelerated to every 8 week dosing, and 5 (2%) subjects were terminated from treatment for non-response.

At Week 40, the subjects who had been responders at Week 28 and remained responders at Week 40 (and had been originally randomized to ustekinumab) were randomly assigned to either continue every 12 week dosing or withdraw treatment. Approximately 90% of subjects who had previously demonstrated the ability to respond to every 12 week dosing of their assigned ustekinumab dose were able to maintain response 12 weeks later (either from Week 28 to 40 or from Week 40 to 52). Approximately 63% of subjects who had previously demonstrated the ability to maintain response through Week 40 but were withdrawn from treatment at Week 40 maintained response through Week 52. See Figure 9.

**Figure 9 – Maintenance of PASI 75 Response among Subjects Responding at Weeks 28 and 40 (Study 08)**



Relatively few subjects in Study 08 were maintained on every 12 week dosing throughout the 52-week reporting period of the study (77/255 (30%) on 45 mg and 85/256 (33%) on 90 mg). The Week 40 dosing status of subjects originally randomized to ustekinumab in Study 08 is presented in Table 14. Subjects could be accelerated to every 8 week dosing at either Week 28 or Week 40. The reporting period for Study 09 was through Week 28.

**Table 14 – Week 40 Dosing Status for Subjects Originally Randomized to Ustekinumab (Study 08)**

Regimen	45 mg	90 mg
	N=255	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%)

## 3.2 Evaluation of Safety

### 3.2.1 Adverse Events

This review only discusses the adverse events observed during the placebo-controlled period (first 12 weeks) of Studies 08 and 09. The incidence of the top 15 most frequently reported adverse events in each study are presented in Table 15 and Table 16. The incidences of the most common events are similar across all three treatment groups (45 mg, 90 mg, and placebo).

**Table 15 – Most Common Adverse Events during the Placebo-Controlled Period (Study 08)**

	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
Subjects with 1 or more events	146 (57.3%)	131 (51.4%)	122 (47.8%)
Nasopharyngitis	26 (10.2%)	21 (8.2%)	22 (8.6%)
Upper respiratory tract infection	18 (7.1%)	16 (6.3%)	16 (6.3%)
Headache	14 (5.5%)	13 (5.1%)	6 (2.4%)
Arthralgia	7 (2.7%)	6 (2.4%)	7 (2.7%)
Back pain	6 (2.4%)	7 (2.7%)	1 (0.4%)
Dizziness	5 (2.0%)	6 (2.4%)	3 (1.2%)
Fatigue	5 (2.0%)	6 (2.4%)	3 (1.2%)
Sinusitis	6 (2.4%)	4 (1.6%)	6 (2.4%)
Hypertension	6 (2.4%)	3 (1.2%)	4 (1.6%)
Gastroenteritis	6 (2.4%)	2 (0.8%)	5 (2.0%)
Psoriasis	2 (0.8%)	6 (2.4%)	3 (1.2%)
Depression	5 (2.0%)	2 (0.8%)	3 (1.2%)
Injection site erythema	0 (0.0%)	7 (2.7%)	2 (0.8%)
Pharyngolaryngeal pain	3 (1.2%)	4 (1.6%)	3 (1.2%)
Viral upper respiratory tract infection	4 (1.6%)	3 (1.2%)	1 (0.4%)

**Table 16 - Most Common Adverse Events during the Placebo-Controlled Period (Study 09)**

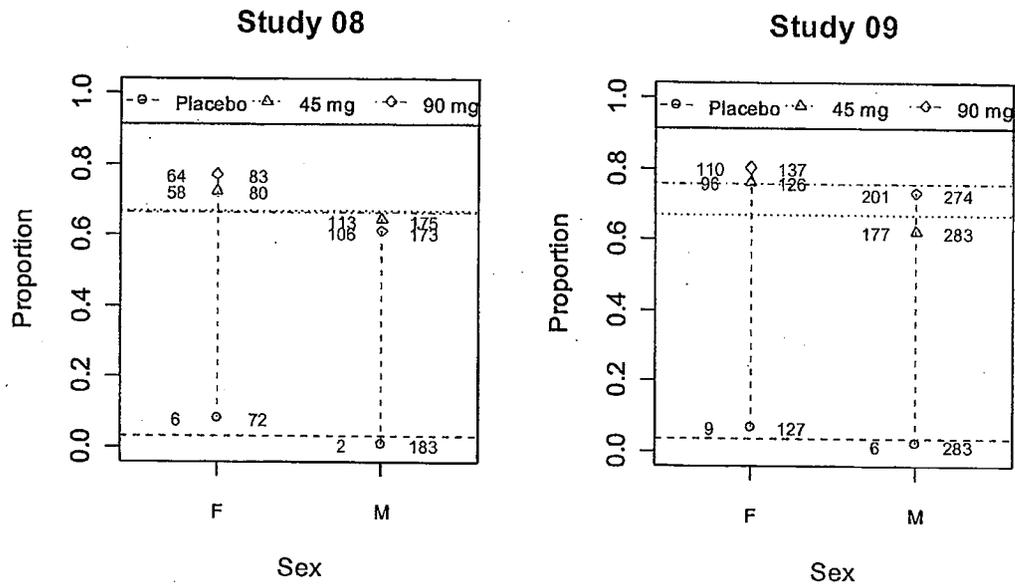
	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
Subjects with 1 or more events	215 (52.6%)	197 (47.9%)	202 (49.3%)
Nasopharyngitis	30 (7.3%)	28 (6.8%)	29 (7.1%)
Headache	19 (4.6%)	19 (4.6%)	17 (4.1%)
Upper respiratory tract infection	18 (4.4%)	12 (2.9%)	14 (3.4%)
Arthralgia	14 (3.4%)	11 (2.7%)	13 (3.2%)
Fatigue	13 (3.2%)	11 (2.7%)	11 (2.7%)
Diarrhoea	9 (2.2%)	11 (2.7%)	11 (2.7%)
Pharyngolaryngeal pain	6 (1.5%)	8 (1.9%)	4 (1.0%)
Pruritus	7 (1.7%)	6 (1.5%)	5 (1.2%)
Injection site erythema	6 (1.5%)	6 (1.5%)	1 (0.2%)
Dizziness	3 (0.7%)	8 (1.9%)	5 (1.2%)
Back pain	3 (0.7%)	7 (1.7%)	7 (1.7%)
Myalgia	5 (1.2%)	5 (1.2%)	3 (0.7%)
Nausea	6 (1.5%)	4 (1.0%)	5 (1.2%)
Hypertension	5 (1.2%)	4 (1.0%)	6 (1.5%)
Sinusitis	3 (0.7%)	5 (1.2%)	4 (1.0%)

## 4 Findings in Special/Subgroup Populations

### 4.1 Gender, Race, and Age

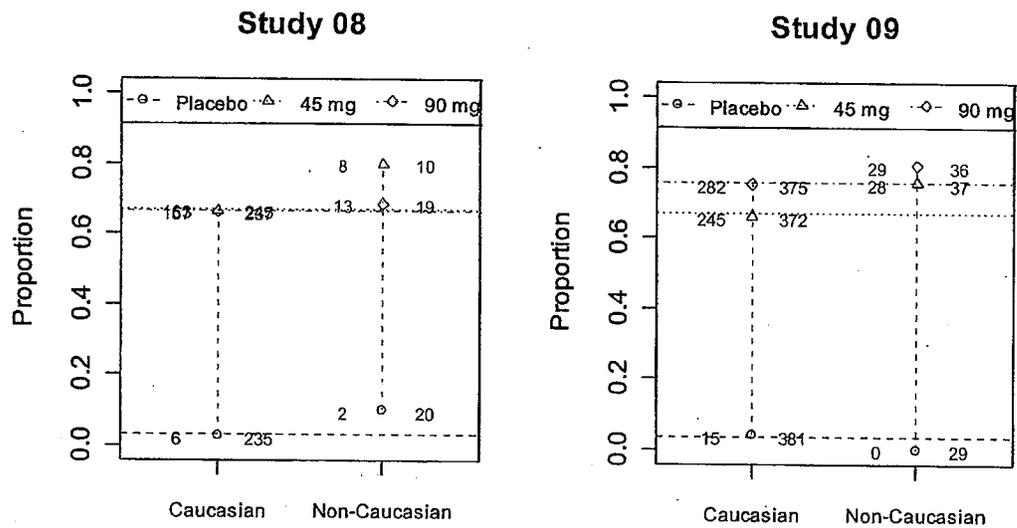
The PASI 75 response rates were similar for both men and women (see Figure 10). The studies enrolled relatively few non-Caucasians and relatively few subjects age 65 and older, so any differences in efficacy for these subgroups would be difficult to detect. The PASI 75 response rates by race (Caucasian vs. non-Caucasian) and age (<65 vs. ≥ 65) are presented in Figure 11 and Figure 12.

Figure 10 – PASI 75 Response Rates at Week 12 by Gender



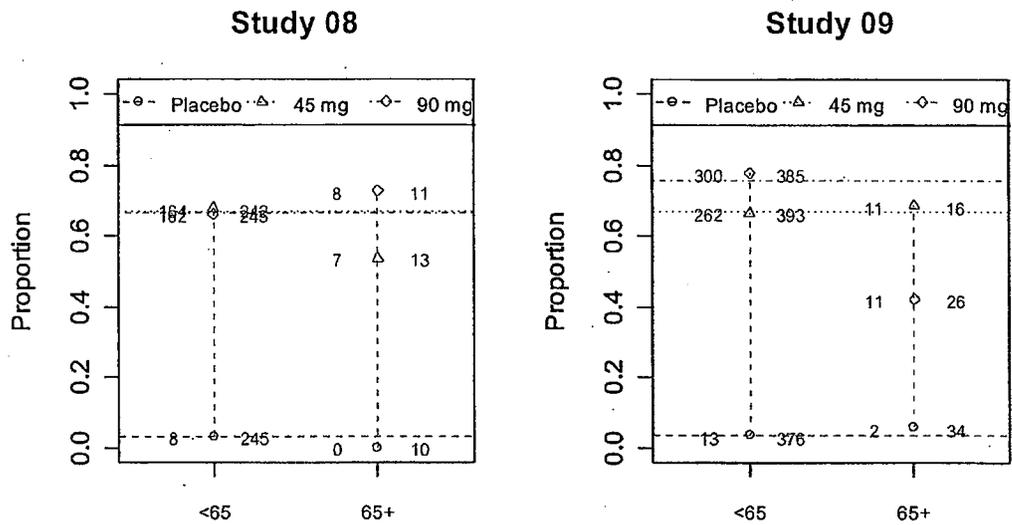
Note: Numbers represent the number of success (on the left) and the number of subjects (on the right) per subgroup.

Figure 11 - PASI 75 Response Rates at Week 12 by Race



Note: Numbers represent the number of success (on the left) and the number of subjects (on the right) per subgroup.

Figure 12 - PASI 75 Response Rates at Week 12 by Age Group

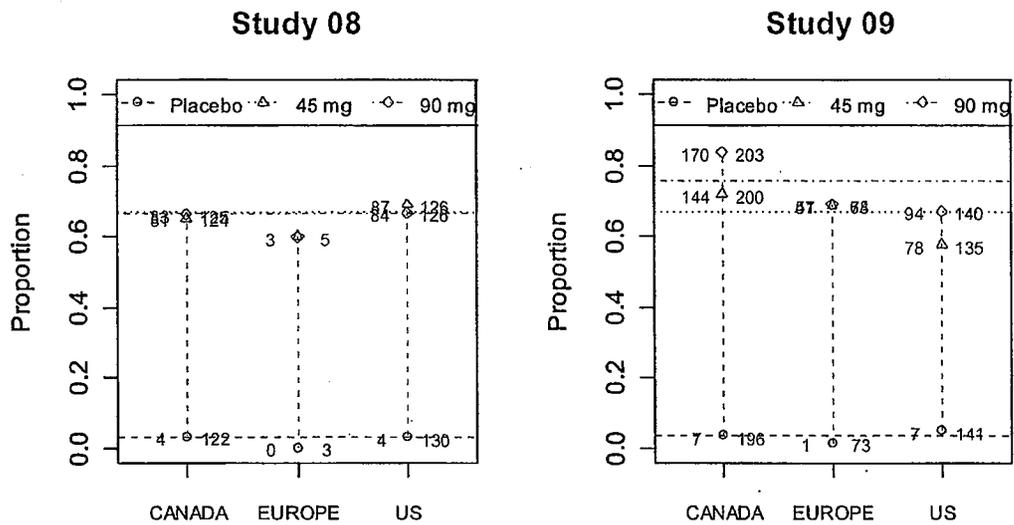


Note: Numbers represent the number of success (on the left) and the number of subjects (on the right) per subgroup.

**4.2 Other Special/Subgroup Populations**

Studies 08 and 09 were conducted in the US, Canada, and Europe. Efficacy was similar in all three regions. Most of the higher efficacy observed on the 90 mg dose in Study 09 was from Canadian centers.

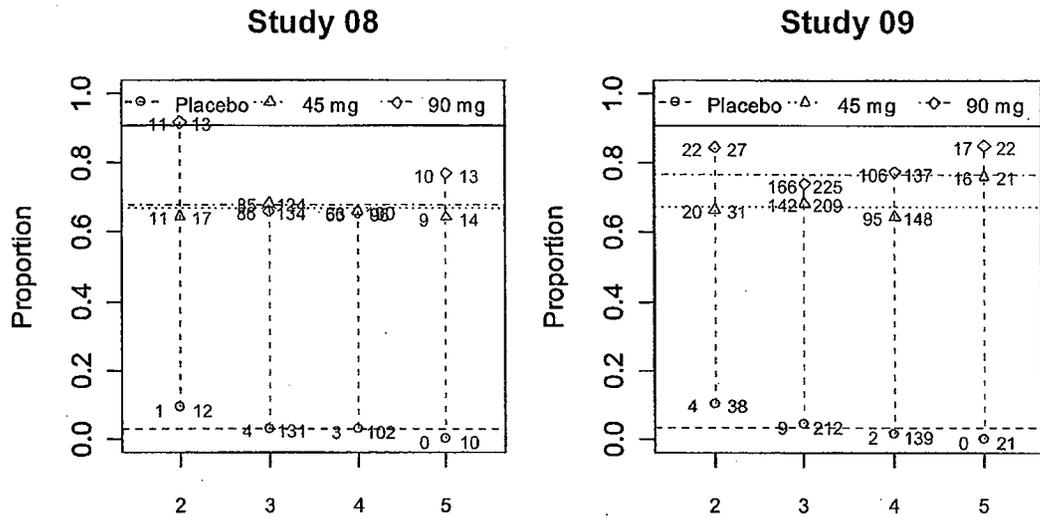
Figure 13 - PASI 75 Response Rates at Week 12 by Country



Note: Numbers represent the number of success (on the left) and the number of subjects (on the right) per subgroup.

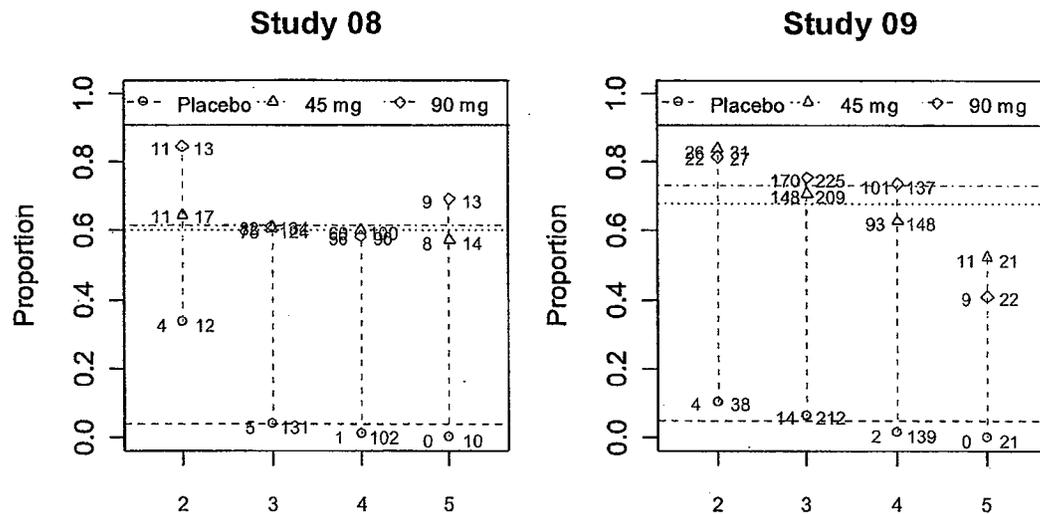
PASI 75 response rates were similar across all levels of the baseline PGA in both studies. See Figure 14. Because PGA response may be directly impacted by baseline PGA, the figures for PGA response by baseline PGA are also presented in Figure 15. Study 08 does not demonstrate any differences in PGA response based on baseline PGA, however, in Study 09, a trend with decreasing response rates with increasing baseline scores is observed.

Figure 14 - PASI 75 Response Rates at Week 12 by Baseline PGA



Note: Numbers represent the number of success (on the left) and the number of subjects (on the right) per subgroup.

Figure 15 - PGA Response Rates at Week 12 by Baseline PGA



Note: Numbers represent the number of success (on the left) and the number of subjects (on the right) per subgroup.

Subgroup analyses by weight can be found in Section 3.1.8, and analyses regarding investigators who participated in both studies can be found in Section 3.1.7.

## 5 Summary and Conclusions

### 5.1 Statistical Issues and Collective Evidence

The clinical studies demonstrated that ustekinumab is efficacious relative to placebo in the treatment of psoriasis. Both studies demonstrated statistical significance for the primary and secondary efficacy endpoints. Results were consistent across studies and endpoints. The PASI 75 response and PGA response results are presented in Table 17.

**Table 17 – Week 12 Efficacy Results**

	Ustekinumab 45 mg	Ustekinumab 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 or 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 or Minimal	278 (68%) p<0.001	302 (73%) p<0.001	20 (5%)

The amount of missing data was relatively small (<4%) at Week 12. Both the 45 mg and the 90 mg dose of ustekinumab had very similar response rates. Although the studies evaluated fixed dosing irrespective of weight, the applicant has proposed that the recommended dosing regimen would be for subjects ≤ 100 kg to use 45 mg and subjects > 100 kg to use 90 mg. Analyses at multiple timepoints and across multiple endpoints in both studies support the assertion selecting a dose based on weight could help maximize efficacy while minimizing total exposure to ustekinumab. Both the 45 mg and 90 mg doses are effective across the full range of subject weights. The weight group with the lowest response rate—subjects weighing over 130 kg—still had PASI 75 response rates of at least 40% on ustekinumab. Thus it appears that any recommended dosing regimen based on weight using doses in the range of 45 to 90 mg would be an effective regimen. However, it appears that much is still not known about how to optimize dose based on weight.

Typically the Division recommends using separate sets of investigators for each pivotal Phase 3 study so that the studies can be considered independent. Studies 08 and 09 had a number of investigators who participated in both studies. Response rates for subjects with investigators who participated in both studies were slightly higher than for those where the investigator participated in only one study. However, these differences were not large, and because of the magnitude of the treatment effect for ustekinumab, efficacy claims are still supported even when only subjects from unique investigators are considered.

Efficacy was generally consistent across most demographic subsets, such as gender and country. The studies enrolled too few non-Caucasians subjects and subjects age 65 and older to compare efficacy across race and age groups. Ustekinumab was effective across the range of baseline severity from moderate to severe.

## **5.2 Conclusions and Recommendations**

The efficacy of ustekinumab 45 mg and 90 mg in the treatment of moderate to severe psoriasis has been demonstrated in two clinical studies (Studies 08 and 09). Efficacy at Week 12 was demonstrated through both the protocol-specified primary endpoint of PASI 75 response and the secondary endpoint of PGA response.

The applicant has proposed that ustekinumab should be dosed initially and 4 weeks later, followed by doses every 12 weeks. In the data submitted by the applicant, subjects in Study 09 were followed through Week 28 (a maximum of 3 doses at Weeks 0, 4, and 16). Subjects in Study 08 were followed through Week 52. After Week 28, subjects received a variable number of doses depending on observed response and randomization assignment. To receive a full year's worth of every 12 week dosing in Study 08, a subject had to maintain PASI 75 response at Weeks 28 and 40 and be randomized to active treatment at Week 40. About 1/3 of the subjects originally randomized to ustekinumab in Study 08 received a full year's worth of every 12 week dosing (77/255 subjects on 45 mg and 85/256 subjects on 90 mg). A comparable proportion were randomized to withdraw treatment at Week 40 (73/255 subjects on 45 mg and 87/256 subjects on 90 mg). The remaining third of subjects were either accelerated to more frequent dosing, terminated for non-response, or dropouts.

The applicant has proposed that subjects weighing 100 kg or less should receive 45 mg at each dosing timepoint and subjects weighing more than 100 kg should receive 90 mg at each dosing timepoint. Although selecting a dose based on weight was not pre-planned by the sponsor, the data do appear to support that weight-based dosing may be appropriate, based on similar efficacy patterns across studies and timepoints. However, the weight-based dosing categories proposed by the sponsor are ad hoc and it is difficult to have any confidence that the sponsor's proposal is in any way an optimal approach.

## **6 Appendix**

### **6.1 Biased Coin Randomization Procedure**

The following information on the randomization algorithm is copied verbatim from the statistical analysis plan (pg 13-14 of file c0743t08-appendix-11.pdf).

Sites will place a phone call to the IVRS to randomize a subject at Week 0 after the informed consent has been obtained and the subject has been successfully screened. Site personnel will be required to respond to several prompts in order for the system to determine stratification characteristics for the subject. The randomization will be stratified by investigational site, weight ( $\leq 90$  kg or  $> 90$  kg), and previous experience with conventional antipsoriatic systemic therapies (inadequate response to, intolerant to, or contraindication to  $< 3$  or  $\geq 3$  therapies: PUVA, MTX, acitretin, cyclosporine). The randomization algorithm will be invoked and a blinded treatment

assignment will be made. The desired balance between treatment groups is 2:2:1:1. The treatment-balancing algorithm will utilize Site (approximately 60 levels), weight (2 levels:  $\leq 90$  kg or  $> 90$  kg), and previous experience with conventional antipsoriatic systemic therapies (2 levels: inadequate response to, intolerant to, or contraindication to  $< 3$  or  $\geq 3$  therapies). The measure used to calculate lack of balance in the minimization algorithm is the Variance. The probability  $p$  of assignment to the treatment with the lowest total imbalance measure will be as follows. These have been calculated to ensure an overall acceptance average of 0.85 taking the unequal ratios into account.

Treatment Group	Acceptance Probability	Rejection Probability			
		CNTO 1275 45 mg	CNTO 1275 90 mg	Placebo to 45 mg	Placebo to 90 mg
CNTO 1275 45 mg	0.862	Rejected	0.069	0.035	0.035
CNTO 1275 90 mg	0.862	0.069	Rejected	0.035	0.035
Placebo to 45 mg	0.827	0.069	0.069	Rejected	0.035
Placebo to 90 mg	0.827	0.069	0.069	0.035	Rejected

That is, if assigning a subject to one of the placebo treatment groups creates the minimum imbalance: this subject should be assigned to this placebo treatment group with probability 0.827, a 0.069 probability for each of the CNTO 1275 treatment groups and a 0.035 probability for the other placebo treatment group.

If assigning a subject to one of the CNTO 1275 treatment groups creates the minimum imbalance: this subject should be assigned to this CNTO 1275 treatment group with probability 0.862, a 0.069 probability for the other CNTO 1275 treatment group and a 0.035 probability for each of the placebo treatment groups.

If there is more than one treatment with the lowest imbalance measure, then the assignments will be made to one of these tied treatments with the total allocation probability of 1 split in proportion with the allocation ratio of the tied treatments. Weights for the balancing factors at Week 0 are Site (2), Weight (1), and Previous Experience with Conventional Antipsoriatic Systemic Therapies (1).

## 6.2 PGA Scale

The following definition of the Physician's Global Assessment (PGA) scale is copied verbatim from the protocol (pg. 71 of file c0743t08-appendix-01.pdf).

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.

**6.3 Applicant's Week 12 Disposition Tables****Table 18 – Subject Disposition (Discontinuing Treatment Prior to Week 12) - (Study 08)**

	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
Number of Subjects	255	256	255
Subjects Discontinuing Treatment prior to Week 12	1 (<1%)	11 (4%)	12 (5%)
Reasons for Treatment Discontinuation			
Never Treated	-	1	-
Adverse Event	-	2	6
Unsatisfactory Therapeutic Effect	-	1	3
Lost to Follow-Up	-	1	1
Other			
Prohibited Medication Use	1	1	-
Inclusion/Exclusion Criteria Violation	-	2	-
Non-compliance	-	1	-
Subject Request	-	2	2

**Table 19 – Subject Disposition (Discontinuing Treatment Prior to Week 12) (Study 09)**

	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
Number of Subjects	409	411	410
Subjects Discontinuing Treatment prior to Week 12	6	9	16
Reasons for Treatment Discontinuation			
Adverse Event	2	5	7
Unsatisfactory Therapeutic Effect	-	-	2
Lost to Follow-Up	3	-	2
Death	-	1	-
Other	1	3	5
Prohibited Medication Use	1	-	-
Inclusion/Exclusion Criteria Violation	-	1	3
Subject Request	-	1	2
Lost to Follow-up	-	1	-

#### 6.4 Approximate BSA Calculation from PASI Components

Body surface area (BSA) involvement was only recorded at baseline. However, the components of the PASI scale can be used to calculate an approximate BSA. The PASI scale records the following for each body region (head, trunk, upper extremities, lower extremities)

- 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

If the values 0 to 6 are mapped to the approximate median of each range (i.e. 0%, 5%, 20%, 40%, 60%, 80%, 95%), and then weighted by the PASI body region weights (10%, 30%, 20%, 40% for head, trunk, upper extremities, lower extremities), this yields an approximate BSA value. For example, a subject with the following PASI involvement data

	Head	Trunk	Upper Extr.	Lower Extr.
PASI Comp. Score	0	2	1	1
Mapped Score	0%	20%	5%	5%
Body Region Weight	0.10	0.30	0.20	0.40

would have an estimated BSA of:  $0.10(0) + 0.30(20) + 0.20(5) + 0.40(5) = 9\%$ .

At baseline in Studies 08 and 09 (where BSA was recorded) the recorded BSA and the estimated BSA using PASI components have correlation of about 0.93.

### Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, PhD  
Date: 7/28/2008

*Kathleen Fritsch* 7/28/08  
*Mohamed Alesh* 7/28/08

Statistical Team Leader: Mohamed Alesh, PhD

cc:

DDDP/Walker  
DDDP/Lindstrom  
DDDP/Carr  
DDDP/Walsh  
OBIO/Nevius  
OBIO/Tiwari  
DBIII/Wilson  
DBIII/Alesh  
DBIII/Fritsch

## STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 125261    Applicant: Centocor  
 Drug Name: Ustekinumab    NDA/BLA Type: 505(b)(1)

Stamp Date: 11/28/07

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?**    Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	Study does include database locks
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

<u>Kaulbi Jara</u>	<u>1/28/08</u>
Reviewing Statistician	Date
<u>Mohamed Alom</u>	<u>1/28/08</u>
Supervisor/Team Leader	Date