

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125261

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Memorandum

To: Susan Walker, M.D. (Division Director HFD-540),
Jill Lindstrom, M.D. (Medical Team Leader) Brenda Carr, M.D. (Medical
Reviewer) and, Sue Kang, Pharm.D. (Project Manager)

From: Abimbola Adebowale, Ph.D. (Clinical Pharmacology Reviewer) (M)

Through: JY Jang-Ik Lee (Secondary Reviewer) and E. Dennis Bashaw, Pharm. D.
(Division Director (Acting Team leader), DCP3)

Date: 06/16/09

Subject: BLA 125261, Stelara® (ustekinumab) Single Use Liquid in Vial, 45
mg/0.5 mL and 90 mg/1.0 mL - Complete Response to a CR letter
submitted on January 9th, 2009 and Response to IR letter dated April 17th,
2009.

Introduction

This re-submission is a complete response to the deficiencies outlined in the Complete Response (CR) letter sent to the applicant by the Agency on December 18th, 2008. The original BLA was submitted on November 28th, 2007 for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. There were no deficiencies with regards to clinical pharmacology included in the CR letter. However, on April 17th, 2009, a clinical pharmacology information request (IR) was sent to the applicant due to some concerns that were raised by the product reviewer (Dr. Laurie Graham) with respect to the presence of high levels of visible particulates in the drug product that was used in some of the clinical trials. The clinical pharmacology request was as follows:

Provide a comparison of the immunogenicity incidence and data collected from all study subjects receiving drug product with particulate matter levels of $\geq C$ compared to those receiving drug product with particulate matter levels of $< C$ ($\leq B$).

Summary of Response to FDA's IR of April 17th, 2009:

The applicant responded to the FDA's IR on May 1st, 2009. A review of their response is discussed below:

The analyses of the impact of levels of particulates on the incidence of immunogenicity were based on the analyses of data from the C0743T09 clinical trial. The applicant stated that all ustekinumab administered in this clinical trial prior to Week 52 had particulate levels $< C$ ($\leq B$). After Week 52, two lots of ustekinumab used in the C0743T09 trial had particulate levels $\geq C$ - Lots 6DS4Z (45 mg) and 6DS50 (90 mg). Drug products from these lots were used in the C0743T09 trials between Weeks 52 and 80 of the trial. The

impact of particulate matter levels in the drug products on the incidence of immunogenicity was analyzed by comparing the antibody status in subjects who received the drug product through week 52 versus subjects who received the drug product through week 88. The data consisted of 1202/1212 (~ 99 %) subjects treated with ustekinumab that had evaluable serum samples for antibodies to ustekinumab. Summary tables of antibody to ustekinumab status through week 52 (Table 1) and through week 88 (Table 2) are inserted below:

Table 1: Summary of antibody to ustekinumab status through Week 52; treated subjects

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

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

^b Denominator is subjects with appropriate samples.

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

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

^e Includes all subjects whose last sample could not be classified as negative due to potential interference from circulating active study agent, and excludes subjects who were positive at any time.

Table 2: Summary of antibody to ustekinumab status through Week 88; subjects treated with ustekinumab

	Ustekinumab		
	45 mg ^a	90 mg ^a	Combined
Subjects treated with ustekinumab	606	606	1212
Subjects with appropriate samples ^b	600	602	1202
Subjects positive for antibodies to ustekinumab at any time ^{c,d}	39 (6.5%)	25 (4.2%)	64 (5.3%)
Subjects negative for antibodies to ustekinumab after last treatment ^{b,c}	561 (93.5%)	577 (95.8%)	1138 (94.7%)

^a Placebo crossover subjects are included after crossover to ustekinumab.

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

^c Denominator is subjects with appropriate samples.

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

^e Includes all subjects whose last sample was negative and those who were 'inconclusive', and excludes subjects who were positive at any time.

* The applicant noted that 1 subject [C0743T09-018-025 (45 mg dose)] was misclassified as negative for antibodies to ustekinumab at Week 88 when he should have been classified as positive. This accounts for the reported decrease in antibody-positive subjects from 65 subjects at Week 52 to 64 subjects at Week 88.

The data in the tables above indicate the following:

- Antibodies to ustekinumab were detected in 65 of 1202 (5.4%) ustekinumab-treated subjects through Week 52 (i.e. before they received any drug with particulate levels $\geq C$).
- No new subjects developed antibodies to ustekinumab after Week 52 and through Week 88 (i.e. after 790 subjects were exposed to ustekinumab with particulate levels $\geq C$).
- Therefore, these results suggest that particulate levels $\geq C$ were not associated with an increase in the incidence of immunogenicity.

Recommendations:

From a clinical pharmacology perspective, the applicant's response to the information request (dated April 17th, 2009) is acceptable. The data provided suggests that the incidence of immunogenicity in study subjects receiving the drug product with particulate matter levels $\geq C$ were comparable to those receiving drug product with particulate matter levels $< C$.

Clinical Pharmacology Review

BLA	STN 125261/0	Submission Date(s)	November 28 th , 2007 and March 25 th , 2008
Brand Name	Pending		
Generic Name	Ustekinumab		
Primary Reviewer	Abimbola Adebawale, Ph.D.		
Secondary Reviewer	Jang-Ik Lee, Pharm.D., Ph.D.		
Pharmacometrics Reviewer	Pravin Jadhav, Ph.D.		
Pharmacometrics Director	Joga Gobburu, Ph.D.		
Pharmacogenomics Reviewers	Shashi Amur, Ph.D. and Padmaja Mummaneni, Ph.D.		
Acting Pharmacogenomics Director and Team Leader	Gilbert Burckart, Pharm. D.		
Division Director of DCP-3	Dennis Bashaw, Pharm.D.		
OCP Division	DCP-3		
OND Division	The Division of Dermal and Dental Products (DDDP) (HFD-540)		
Applicant	Centocor Inc., Malvern, PA		
Submission Type; Code	Original BLA	NME	
Formulation; Strength(s)	Liquid in vial for subcutaneous injection.	45 mg/ 0.5 mL vial and 90 mg/ 1.0 mL vial	
Proposed Indication	Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy		
Proposed Dosing Regimen	Patients weighing \leq 100 kg, 45 mg initially and 4 weeks later, followed by dosing every 12 weeks Patients weighing $>$ 100 kg, 90 mg initially and 4 weeks later, followed by dosing every 12 weeks.		

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1 Executive Summary

Ustekinumab is a first-in-class new molecular entity proposed for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. This biologic product is a fully human immunoglobulin (Ig) G1 monoclonal antibody (mAb) that binds to the p40 protein subunit of human interleukins (IL), IL-12 and IL-23. IL-12 and IL-23 are comprised of a shared p40 subunit and a subunit that is unique to each cytokine, p35 for IL-12 and p19 for IL-23. The contribution of IL-12 and IL-23 to the psoriatic process is still being elucidated. Ustekinumab has not been previously approved for use in the U.S. for any indication.

The risk/benefit analysis of Ustekinumab for the proposed psoriasis indication in this submission was discussed at a Dermatology Advisory Committee (AC) meeting held on June 17th, 2008. At the AC meeting, Dr. Pravin Jadhav (the Pharmacometrics Reviewer) presented data on alternative weight-based dosing paradigms (i.e., 3 step dosing regimen). The applicant's two step dosing proposal was recommended by 7 votes versus 3 votes for the three step dosing proposal. The main concerns from the committee were as follows: (1) lack of data at 67.5 mg (2) possible delays in generating stability data for 67.5 mg and (3) lack of availability of information on the lowest effective dose. However, it is noted that the AC was not impressed with the applicant's reasoning for not exploring the 3 step dosing regimen.

The applicant stated that ustekinumab is currently being studied in other indications including multiple sclerosis (MS), Crohn's disease (CD), and psoriatic arthritis (PsA).

1.1 Recommendations

The clinical pharmacology and biopharmaceutics information provided in this submission is acceptable provided that the applicant adequately addresses the following recommendations:

Pharmacometrics

Based on exposure-response analyses, the following 3-step dosing regimen is recommended:

- a. For patients weighing < 70 kg (154 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by dosing every 12 weeks.
- b. For patients weighing \geq 70 kg and < 100 kg (220 lbs), the recommended dose is 67.5 mg initially and 4 weeks later, followed by dosing every 12 weeks.
- c. For patients weighing \geq 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by dosing every 12 weeks.

Labeling Recommendations

We have labeling recommendations for pharmacokinetics, drug-drug interactions, immunogenicity, and pharmacogenomics in Section 3 (page # 41) and Section 4 (incorporated into the proposed package insert on page # 42) that need to be conveyed to the applicant.

1.1.1 Comments to be conveyed to the applicant:

We recommend that the sponsor continues the search for efficacy biomarkers in the context of ustekinumab with emphasis on reproducibility of the findings and correlation to the clinical end point. Early identification of non-responders through the use of biomarkers would benefit the clinicians and patients.

If the sponsor opts to get scientific advice from FDA on exploratory data that are not required to be submitted as an IND, it is possible to use the voluntary exploratory data submission (VXDX) process.

Please refer to <http://www.fda.gov/Cder/guidance/6400fnl.pdf>

For qualification of biomarkers (disease or diagnostic biomarkers/efficacy- or safety-related biomarkers), a pilot process for biomarker qualification is also available.

1.2 Phase IV Commitments

Drug-Drug Interaction:

Cytokines such as interleukin (IL)-2, IL-6 and IL-10 are known to downregulate the expression of cytochrome P450 enzymes (CYP) in humans and inhibit the metabolism of CYP substrates. On the contrary, cytokine antagonists such as basiliximab (anti-IL-2 receptor antibody) and tocilizumab (anti-IL-6 receptor antibody, [internal comment, pending approval]) are known to reverse the effect of the cytokines on CYP substrates, resulting in a "normalization" of CYP regulation. As a disease state, psoriatic patients have elevated cytokine levels. Ustekinumab as an IL-12/IL-23 antagonist has the potential to reverse any IL-12/IL-23 cytokine mediated CYP suppression. Thus in psoriasis patients who have been stabilized on drugs with CYP mediated metabolism, ustekinumab has the potential, through this normalization of CYP activity to require dose adjustment. Please conduct an in vitro study or studies to determine whether IL-12 and/or IL-23 modulate CYP enzyme expression and whether ustekinumab is able to reverse the effects of IL-12/IL-23 on CYP expression (e.g., in vitro hepatocyte study). An alternative in vivo approach would be to determine the potential of ustekinumab for the alteration of CYP substrate metabolism in psoriasis patients (e.g., a cocktail study with CYP probe drugs).

Immunogenicity:

The currently submitted data does not allow for the determination of the true incidence rate of a positive immune response to ustekinumab in the psoriasis subjects. At the Advisory Committee meeting that was held on June 17th, 2008, the medical reviewer, Dr. Brenda Carr made some recommendations with regards to the possible future approaches to immunogenicity testing based on the fact that the antibody status was inconclusive in up to 90 % of the psoriasis subjects in the pivotal Phase 3 trials. The recommendations were as follows:

Possible clarifying investigations of immunogenicity of ustekinumab include:

- *A clinical trial in which immunogenicity testing is done at time points that have allowed for clearance of ustekinumab*
- *Development of an assay with which the presence of ustekinumab does not interfere*

According to the applicant's presentation at the Advisory Committee meeting, more immunogenicity samples were collected after ustekinumab had been held or discontinued in a pivotal clinical trial(s) and the samples could provide more conclusive results. An information request (IR) was sent to Centocor to provide this additional immunogenicity data for review by the Division of Dermal and Dental Products (DDDP) prior to the approval action of this BLA. DDDP is currently awaiting the response from the applicant.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The clinical pharmacology development program for psoriasis consisted of 5 studies (C0379T01, C0379T02, C0379T04, C0743T08 and C0743T09) conducted in psoriasis subjects (PS) and, 1 study (C0743T11) conducted in healthy subjects.

- C0379T01 and C0379T02 were Phase 1 psoriasis studies examining single intravenous (IV) and subcutaneous (SC) administration, respectively, of weight adjusted doses (doses of CNTO1275 ranging from 0.09 mg/kg – 4.5 mg/kg).
- C0379T04 was a Phase 2 psoriasis study examining single (45 mg and 90 mg doses) and multiple fixed doses (45 mg and 90 mg doses weekly x 4) of a reconstituted lyophilized formulation of CNTO 1275 given by SC administration.
- The 2 pivotal Phase 3 psoriasis studies C0743T08 [PHOENIX 1] and C0743T09 [PHOENIX 2] examined the formulation and dosing regimens (45 mg and 90 mg SC at Week 0, 4, and then q12 w) intended for the commercial product.
- The single pharmacokinetics (PK) study C0743T11 conducted in healthy subjects examined a single dose of the highest proposed dose strength (90 mg SC) of the formulation intended for the commercial product.

The PK of CNTO 1275 following intense blood sampling was characterized in psoriasis subjects in studies C0379T01 (IV administration), C0379T02 (SC administration) and C0379T04 (SC), and in healthy subjects in study C0743T11 (SC). The PK of CNTO 1275 was also characterized in Phase 3 studies (C0743T08 and C0743T09) following sparse sampling in psoriasis subjects. A population PK modeling approach was used to analyze the serum CNTO 1275 concentrations in the Phase 3 studies.

Please note that in this submission, ustekinumab was also referred to as CNTO 1275, CNTO 1275 monoclonal antibody, 12B75, 12B75 IgG, anti-IL-12, human anti-IL-12 monoclonal antibody, human anti-IL-12 IgG1 monoclonal antibody, anti-IL-12p40, IL-12/23 monoclonal antibody, and anti-IL-12/23p40. These terms were used interchangeably in the review as well.

Exposure-Response Analysis:

Ustekinumab AUC-PASI75 response rate analysis was used to evaluate the sponsor's dosing proposal (45 mg for ≤ 100 kg subjects and 90 mg for >100 kg subjects). The key findings of the analysis were as follows:

1. Psoriasis improvement is dependent on serum ustekinumab concentration or AUC.
2. At a given dose, serum concentrations (and AUCs) in heavier (median body weight 117 kg) subjects are 50% compared to those in lighter subjects (median body weight 68 kg).
3. Due to PK differences, the (PASI75) response rate in heavier subject is lower than response rate in lighter subjects.

Based on AUC-PASI response rate analysis, different body weight based dosing adjustments were explored. Each of the dosing strategies explored offer different

advantages. Weight based dosing strategy is needed to maximize response rates and the choice should depend on benefit-risk assessment of CNTO 1275.

Pharmacokinetics of Ustekinumab:

Absorption:

In healthy subjects (C0743T11), the median T_{max} occurred approximately 8.5 days after a single 90 mg SC administration. This was comparable to the median T_{max} of 7 to 14 days obtained in subjects with psoriasis (C037902; approximate dose ranging from 24 to 240 mg and C037904; dose = 45 mg and 90 mg) following a single SC administration of ustekinumab. Based on a cross-study comparison of data between studies C0379T01 (IV) and C0379T02 (SC), the absolute bioavailability (F) of CNTO 1275 was estimated to be 57.2% (ranging from 24.4 % to 95.0 %) following a single SC administration (0.27 mg/kg to 2.7 mg/kg, or ~ 24 to 240 mg based on a median body weight of 90 kg in psoriasis subjects).

Distribution:

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

Metabolism:

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

Elimination

In healthy subjects, the mean (SD) terminal half-life (t_{1/2}) obtained after a single 90 mg dose administration (C743T11) was 22.1 (12.1) days. In psoriasis subjects, the mean (SD) terminal half-life after a single SC administration (C0379T02; dose = 24 to 240 mg and, C0379T04, dose = 45 mg and 90 mg) was from 14.9 (4.6) to 45.6 (80.2) days. The mean (SD) t_{1/2} after multiple SC administrations (C0379T04) of 45 mg and 90 mg was 24.9 (7.9) days and 28.1 (7.3) days, respectively.

The mean (SD) apparent systemic clearance (CL/F) following a single SC administration of 90 mg of ustekinumab was 3.1 (1.1) mL/day/kg in healthy subjects (C0743T11). The mean (SD) CL/F following a single SC administration ranged from approximately 3.4 (1.7) to 5.8 (3.5) mL/day/kg in psoriasis subjects (C0379T02, dose = 24 to 240 mg and, C0379T04, dose = 45 mg and 90 mg).

Dose Proportionality after Single- and Multiple-Dose Administration:

The C_{max} and AUC values increased in an approximately dose-proportional manner in subjects with psoriasis (C0379T02) after a single SC administration at doses ranging from 0.27 to 2.7 mg/kg (approximately 24 mg to 240 mg of ustekinumab based on an assumed body weight of 90 kg in psoriasis subjects). The doses selected for the Phase 3 studies fell within this dose proportional range (i.e. 45 mg and 90 mg).

A dose-proportionality in serum CNTO 1275 concentrations was observed in each of the two Phase 3 studies (C0743T08 and C0743T09). Serum CNTO 1275 concentrations were higher in the 90 mg dose group compared to the 45 mg dose group, with differences between the two groups showing dose proportionality.

Achievement of Steady State:

Steady state was achieved by Week 28. The mean (SD) steady-state trough serum concentrations at Week 28 in study C0743T08 and C0743T09 was 0.33 (0.74) µg/mL and 0.31 (0.33) µg/mL, respectively (45 mg every 12 weeks), and 0.059 (0.60) µg/mL and 0.64 (0.64) µg/mL respectively, (90 mg every 12 weeks). There was no evidence of accumulation in CNTO 1275 serum concentrations over time when given SC every 12 weeks.

Intrinsic Factors

The effects of intrinsic and extrinsic factors on pharmacokinetics of CNTO 1275 were not studied in separate clinical trials but as part of the population PK analysis.

Weight:

Serum CNTO 1275 concentrations were affected by subject weight in studies C0743T08 and C0743T09. Generally, within each dose (45 mg and 90 mg) subjects with higher weights > 100 kg had lower (30 % to 60 %) median trough serum CNTO 1275 concentrations compared with subjects with lower weights ≤ 100 kg.

Immunogenicity:

It appears that immunogenicity affects the serum concentrations in one of the phase 3 trials (C0743T08). In this study, the antibody positive patients had serum concentrations that were below the limit of quantitation (LOQ) from week 12 onwards, compared to the antibody negative patients who had serum concentrations of ustekinumab above the LOQ through week 28. This finding was not found to be consistent in the second Phase 3 trial (C0743T09). The inconsistency appears to be due to a small number of confirmed antibody positive/negative patients in Study C0743T09 and the limitation that antibody negativity can be confirmed only when ustekinumab concentrations are not measurable.

The effect of immunogenicity on the CL/F of ustekinumab was evaluated in the population PK analysis. According to the analysis, there were 62 subjects (3%) in the combined dataset who had a positive immune response to ustekinumab over the course of treatment with ustekinumab. The model-predicted mean CL/F value for ustekinumab was 35.5% higher in subjects with positive immune response to ustekinumab than that in subjects with other immune responses (i.e., negative or inconclusive). However, because only a small number of subjects were determined to be positive, the potential impact of

immunogenicity on the pharmacokinetics of ustekinumab should be interpreted with caution and requires further investigation.

The interpretation of this data is limited by the following reasons:

- The true incidence rate of the antibodies to ustekinumab in psoriasis subjects could not be determined from the data provided because of the limitations of the antibody assay method. One important limitation of the assay used to assess for antibodies to ustekinumab is the potential for assay interference by ustekinumab itself. Thus, a true determination of a subject's antibody to ustekinumab status can only occur after sufficient time has passed to allow a subject to clear ustekinumab ("wash-out" period). The subjects classified as inconclusives had detectable levels of ustekinumab present which precluded a definitive assessment of their antibody status.
- The low incidence of antibody-positive subjects in the clinical studies (5.1 % (38/743 subjects) in C0743T08 and 2.8 % (33/1198) in C0743T09) and the high percentage of inconclusive subjects (47.6 % (354/743) in C0743T08 and 89.7 % (1075/1198) in C0743T09). This high incidence of inconclusives precludes definitive conclusions on the impact of antibody status on the pharmacokinetics, pharmacodynamics and the clinical response of ustekinumab.

The applicant stated that the concern for assay interference by ustekinumab in the antibody assay was addressed in C0379T04, a Phase 2 study, in which psoriasis subjects were administered a limited number (1 to 5 doses) of SC administrations, and then followed through 52 weeks to allow antibody assessment after an adequate wash-out period. The incidence of antibody-positive subjects in the Phase 2 study was 4.1 % (12/293) and the percentage of inconclusive subjects were 10.6 % (31/293).

A comparison of the data obtained in the Phase 2 and 3 studies indicates that the percentage of subjects with an inconclusive antibody status did decrease considerably when adequate wash-out period is allowed. However, it may not be appropriate to extrapolate the data obtained in the Phase 2 studies since the dosing regimen used is different from that used in the Phase 3 trials and this may impact the incidence rate of the antibodies to ustekinumab.

Effect of Diabetes Co-morbidity:

There were 206 subjects (10.6%) with diabetes co-morbidity included in the population PK analysis. In a one-compartmental population PK analysis, the model-predicted mean CL/F and V/F values for ustekinumab were 28.7% and 13.2%, respectively, higher in subjects with diabetes. The impact on PASI75 response of differences in ustekinumab exposure due to diabetes co-morbidity was evaluated. In the data relevant to the proposed dosing recommendations (45 mg for <100 kg subjects and 90 mg for ≥100 kg), the proportion of PASI75 responders was lower in subjects with diabetes history or existing

condition. For example, 59.5% (N=37) vs 75.5% (N=421) at 45 mg for <100 Kg and 65.5% (N=29) vs 73.1% (N=193) at 90 mg for \geq 100 kg. The response rate in all subgroups was at least 60%, however, the number of subjects with diabetes were much less to allow for an interpretation of precise differences. Higher difference was seen in the 45 mg group for <100 kg subjects, the recommended 3 step dosing proposal might reduce these differences as patients with diabetes will receive 67.5 mg leading to higher ustekinumab levels. Dosing change based on diabetes co-morbidity is not recommended at this time.

Extrinsic Factors

Drug-Drug Interactions:

IgG antibodies are not metabolized by cytochrome P450 enzymes (CYP). Therefore, direct pharmacokinetic interactions via the CYP pathway is not expected between ustekinumab and co-administered small molecular weight drugs. Potential drug-drug interactions were evaluated using a population pharmacokinetic approach among the 28 most frequently used concomitant medications (including atorvastatin, metformin, acetylsalicylic acid, ibuprofen, and paracetamol) in the Phase 3 studies. None of the concomitant medications had a significant effect upon the apparent clearance of ustekinumab. No immunosuppressants were allowed to be used concomitantly in either study.

Ustekinumab, however, might indirectly influence the expression level of CYP enzymes by antagonizing cytokine activities in psoriasis patients because cytokines are known to reduce the expression level of multiple CYP enzymes. Therefore, it is postulated that ustekinumab may increase CYP expression to baseline levels in psoriasis patients leading to decreased exposure of drugs that are metabolized by CYP enzymes. The applicant did not conduct any specific drug interaction studies to evaluate the effect of ustekinumab on CYP expression levels. The current recommendation is to ask the applicant to address this by including the suggested wording in Section 3 (labeling recommendations) based on the approved label for rilonacept (IL-1 antagonist) and the proposed label for tocilizumab (IL-6 antagonist).

QT Prolongation

Thorough QT prolongation studies were not conducted based on recommendations provided to the applicant during the IND stage by the CDER DCRP QT Interdisciplinary Review Team (QT-IRT). The comments provided by the QT-IRT were that monoclonal antibodies do not need to be evaluated in a thorough clinical QT study because as large molecules, monoclonal antibodies cannot access the hERG pore via the intracellular side, which is the target site for most small-molecule QT-prolonging drugs; and monoclonal antibodies can have off-target cardiac effects but QT prolongation has not been observed. The QT-IRT did recommend that routine ECG monitoring in clinical studies should be performed to capture any important effects. The applicant incorporated ECG evaluation in their clinical studies (confirmed with the medical reviewer, Dr. Brenda Carr) and, also

proposes to perform further characterization of the potential impact of CNTO 1275 on cardiovascular risk in a greater number of patients as part of their Risk Management Plan.

Pharmacogenomics:

Pharmacogenomic and Pharmacodynamic assessments (immune response and biomarker data) were included as part of the clinical studies. Three exploratory studies were submitted that contained exploratory gene expression data: Phase I CSR C0379T01, C0379T02 and Phase II CSR C0379T04. In addition, a publication in the Journal of Immunology was also submitted to support the findings from the studies. Two of the exploratory studies employed cDNA microarray technology to identify potential biomarkers of efficacy of CNTO 1275. Additionally, an attempt was made to identify the mechanism of action of the drug and to understand the molecular underpinnings of the pathological process involved in psoriasis. The microarray data assisted in the identification of potential biomarkers for the efficacy of CNTO 1275. Since the microarray data is of exploratory nature and yields a number of false positives, potential biomarkers need to be verified by other technologies such as quantitative real time RT-PCR.

The PCR data obtained with limited number of samples, suggests a correlation of reduced levels of some inflammatory cytokines and chemokines with CNTO 1275 treatment. However, consistency of these findings was not tested in more than one exploratory study. The exception is IL-12p40 mRNA. In two of the studies, a significant reduction in the IL-12p40 mRNA has been reported with CNTO 1275 treatment. However, statistically significant difference in the IL-12p40 mRNA levels was not observed in the third study that examined the samples at week 0 and week 12.

In conclusion, exploratory biomarkers for CNTO 1275 efficacy have been identified in the studies.

Pharmacodynamics

Histological analyses were conducted in the Phase 2 psoriasis study C0379T04 to evaluate the effects of ustekinumab on histological measures of psoriasis including epidermal thickness and keratinocytes cell proliferation (based on an evaluation of Ki67-positive cells, a marker of cell proliferation). The results of the exploratory histological analysis of the psoriatic lesions support the hypothesis that treatment with CNTO 1275 causes a reduction in the local inflammatory infiltrate in psoriatic lesions and epidermal hyperplasia. However, the relationship of these observations to clinical efficacy data is not well defined.

An evaluation of the effect of CNTO 1275 on the systemic circulating serum chemokine/cytokine levels hypothesized to be associated with psoriasis and T-lymphocyte surface markers reflective of immune status were also evaluated in the psoriasis studies C0379T02 and C0379T04. There were no apparent effects on the systemic circulating serum concentrations of chemokine/cytokine hypothesized to be associated with psoriasis following treatment with CNTO 1275. There was also no

apparent effect on the major T lymphocyte populations reflective of immune status examined after treatment with CNTO 1275.

Product Development and Comparability among Product Lots

During the clinical development of CNTO 1275, 2 sources ██████████ of clinical material and different formulations were studied. The to-be-marketed formulation that was used in the Phase 3 psoriasis trials (C0743T08 and C0743T09) and, a clinical pharmacology study (C0743T11) conducted in healthy volunteers consisted of ustekinumab produced by the ██████ cell line. However, for the Phase 1 and 2 studies (C0379T01, C0379T02 and C0379T04) the study agent was produced from cell line ██████████

b(4)

The product reviewer, Dr. Laurie Graham reviewed the product comparability of the different cell lines and formulations used in the clinical studies. The decisions on comparability were based on cumulative product quality data, and the non-clinical PK studies. No clinical PK studies were performed to assess the comparability of ustekinumab. Dr. Laurie indicated that the comparability data presented in the BLA supports comparability between all cell lines and formulations used. See product review for further details.

Signatures:

Primary Reviewer:

Abimbola Adebawale August 1st, 2008

Abimbola Adebawale, Ph.D.,
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Division of Clinical Pharmacology 3,
Office of Clinical Pharmacology

The secondary reviewer concurs with the primary reviewer's Executive Summary.

Division Director:

CAPT E. Dennis Bashaw 8/4/08

CAPT E. Dennis Bashaw, PharmD.
Director, Division of Clinical Pharmacology-3
Office of Clinical Pharmacology

I concur in the 3 tier dosing recommendations and in the requested phase 4 requests related to ADI's + communication.

Note that the signatures for the Pharmacometrics Reviewer and Team Leader and the Pharmacogenomics Reviewer and Team Leader are included in their respective reviews (see attached).

2 Question-Based Review

2.1 General Attributes of the drug

Q What are the highlights of the chemistry and physical-chemical properties of the drug substance?

Ustekinumab is a human κ -type immunoglobulin G1 (IgG1) monoclonal antibody (mAb) with an approximate molecular weight of 148,600 Daltons. It is composed of 2 identical heavy chains and 2 identical kappa (κ) light chains that are covalently linked by disulfide bonds and are non-covalently associated by various (hydrogen bonding, etc.) heavy-heavy and heavy-light chain reactions as shown in Figure 1 below.



b(4)

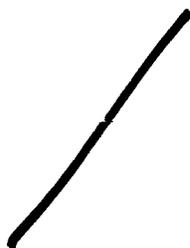


Figure 1 General structure of CNTO 1275 IgG1. The heavy (black) and light (gray)



light chain.)

b(4)

Q What are the therapeutic indication(s) and proposed mechanism(s) of action?

The proposed indication of ustekinumab is for the treatment of adults with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Psoriasis is a chronic, immune-mediated inflammatory skin disease. It is usually characterized by inflammation and keratinocytes hyperproliferation. The etiology of the disease is not completely understood.

Ustekinumab is classified as an interleukin inhibitor. Ustekinumab is reported to have an anti-IL-12/23p40 mechanism of action. IL-12 and IL-23 are heterodimeric cytokines comprised of a shared p40 subunit and a subunit unique to each cytokine, p35 for IL-12 and p19 for IL-23. Ustekinumab binds to the shared p40 protein subunit of human IL-12 and IL-23 thereby blocking p40 from binding to IL-12/IL-23 receptors expressed on the surface of immune cells. Through this mechanism of action, ustekinumab inhibits IL-12 and IL-23-mediated cellular responses. Psoriasis is a T cell-dependent autoimmune disease of the skin. The available information suggests that ustekinumab acts by preventing these cytokines (IL-12 and IL-23) from differentiating and activating T helper (Th) 1 and (Th17) cell mediated psoriatic inflammation.

There are currently 5 FDA approved biologic therapeutics for the treatment of psoriasis: Alefacept (Amevive), Efalizumab (Raptiva), Infliximab (Remicade), Etanercept (Enbrel) and Adalimumab (Humira). Amevive and Raptiva target the T cell surface receptors CD2 and LFA-1, respectively, and act as T cell immunosuppressive agents. Remicade, Enbrel and Humira target and inhibit tumor necrosis factor alfa (TNF α), an inflammatory cytokine produced during psoriasis.

Q What are the proposed route(s) of administration and dosing regimen?

Ustekinumab is intended to be administered by subcutaneous (SC) injection. The proposed dosing regimen is as follows:

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

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

(Refer to page 20 for clinical pharmacologists' proposed dosing regimen)

2.2 General Clinical Pharmacology

Q What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Table 1 Psoriasis Clinical Studies		
Study Total follow-up	Study Design (Severity of Plaque Psoriasis)	Treatment Group (# of subjects)
PHASE 1		
C0379T01 16 weeks	Multicenter, open-label, single IV dose-ascending, nonrandomized, first-in-human study. Subjects had BSA involvement \geq 3% (moderate to severe psoriasis)	Weight adjusted doses: 0.09 mg/kg single IV dose (n = 4) 0.27 mg/kg single IV dose (n = 4) 0.9 mg/kg single IV dose (n = 5) 4.5 mg/kg single IV dose (n = 5)
C0379T02 24 weeks	Multicenter, randomized, double-blind, placebo-controlled single SC dose study. Subjects had BSA involvement \geq 3% (moderate to severe psoriasis)	Weight adjusted doses: Placebo (n = 4) 0.27 mg/kg single SC dose (n = 5) 0.675 mg/kg single SC dose (n = 4) 1.35 mg/kg single SC dose (n = 4) 2.7 mg/kg single SC dose (n = 4)
PHASE 2		
C0379T04 52 weeks	Multicenter, randomized, double-blind, placebo-controlled, parallel study of single and multiple SC dose regimens with 2 fixed doses (45 mg and 90 mg). Subjects had PASI \geq 12 and BSA involvement \geq 10% (moderate to severe psoriasis)	Fixed doses: Placebo (n = 64) ^a Placebo \rightarrow 90 mg single SC dose (n = 47) 45 mg single SC dose (n = 64) 90 mg single SC dose (n = 64) 45 mg weekly x 4 SC doses (n = 64) 90 mg weekly x 4 SC doses (n = 64)
PHASE 3		
C0743T08 (PHOENIX 1) \geq 52 weeks	Multicenter, randomized, double-blind, placebo-controlled, parallel trial of SC administrations in subjects with PASI \geq 12 and BSA involvement \geq 10% (moderate to severe plaque psoriasis)	Fixed doses: Placebo (n = 255) Placebo \rightarrow 45 mg regimen ^d (n = 123) - Placebo \rightarrow 90 mg regimen ^d (n = 120) 45 mg SC Weeks 0, 4 then q12w (n = 255) 90 mg SC Weeks 0, 4 then q12w (n = 256)
C0743T09 (PHOENIX 2) 28 weeks	Multicenter, randomized, double-blind, placebo-controlled, parallel trial of SC administrations in subjects with PASI \geq 12; BSA involvement \geq 10% (moderate to severe plaque psoriasis)	Fixed doses: Placebo (n = 410) Placebo \rightarrow 45 mg regimen ^d (n = 197) - Placebo \rightarrow 90 mg regimen ^d (n = 195) 45 mg SC Weeks 0, 4 then q12w (n = 409) 90 mg SC Weeks 0, 4 then q12w (n = 411)

BSA = body surface area; IV = intravenous; SC = subcutaneous; PASI = Psoriasis Area and Severity Index; q12w = every 12 weeks.

^a At Week 20, subjects in the placebo group received a single dose of 90 mg.

^b Includes all data available through the date the last subject completed the Week 52 visit (i.e., through the end of the reporting period).

^c The placebo groups crossed over to receive 45 mg or 90 mg at Weeks 12 and 16 then q12w.

Q *What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?*

Clinical Endpoints:

The primary endpoint was the proportion of subjects who achieve a $\geq 75\%$ improvement in Psoriasis Area and Severity Index (PASI) from baseline (PASI 75 response) at Week 12. The PASI is an index used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72, on which higher scores represent more severe disease. The PASI score provides a composite assessment of both the severity of the psoriatic lesions and the degree to which the body surface is affected. The severity of the disease is calculated as follows: In the PASI system, the body is divided into 4 regions: the head, trunk, upper extremities, and lower extremities, which account for 10%, 30%, 20%, and 40% of the total body surface area (BSA), respectively. Each of these areas is assessed separately for erythema, induration, and scaling, which are rated on a scale of 0 to 4 (0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe) and for area of involvement, which is rated on a scale of 0 to 6 (0=no involvement and 6 = 100% involvement).

An additional efficacy endpoint was the Physician's Global Assessment (PGA) which documents the physician's assessment of the subject's psoriasis status at a given time-point. Consideration is usually given to the overall plaque elevation, scaling, and erythema observed. The PGA was assessed relative to baseline conditions and is defined as follows: (1) = clear (some residual pigmentation), (2) = excellent (marked improvement), (3) = good (moderate improvement), (4) = fair (slight improvement), (5) = poor (little or no change in scaling, erythema and plaque elevation) and (6) = worse.

Pharmacodynamics (PD):

Exploratory PD assessments were included as part of the 3 of the clinical studies (C0379T01, C0379T02 and C0379T04) conducted in psoriasis patients. One study performed histological and molecular analyses of psoriatic skin biopsies. The effects of ustekinumab on histological measures of psoriasis including epidermal thickness and keratinocytes cell proliferation (based on an evaluation of Ki67-positive cells, a marker of cell proliferation). The basis of this is that psoriatic lesions are characterized by thickened epidermal layers which results from excessive keratinocyte cell proliferation. Therefore, psoriatic disease resolution at a histological level as characterized by a thinning of the epidermal layer and an absence of rete (epidermal) ridges can be used to understand the effects of ustekinumab on psoriatic skin.

Additionally, an attempt was made to identify the mechanism of action of ustekinumab and also to identify treatment-specific markers that correlated with efficacy. Two of the exploratory studies employed cDNA microarray technology to identify potential

biomarkers of efficacy of ustekinumab. In addition, the levels of a limited number of serum immune mediators (cytokines and chemokines e.g. interleukin-2 (IL-2), interleukin-4 (IL-4), known or hypothesized to be associated with psoriasis or the IL-12/IL-23 pathway were also measured in the Phase 1 and 2 studies. T lymphocyte surface markers (CD3, CD4, and CD8) reflective of immune status including CD45RA (naïve), CD45RO (memory), HLA-DR, CD25 and CD69 phenotypes were also measured in these exploratory studies.

Q *Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships of ustekinumab?*

Yes, the active moieties were appropriately identified and measured in serum (see Section 2.6 for further details).

Exposure-Response Evaluation

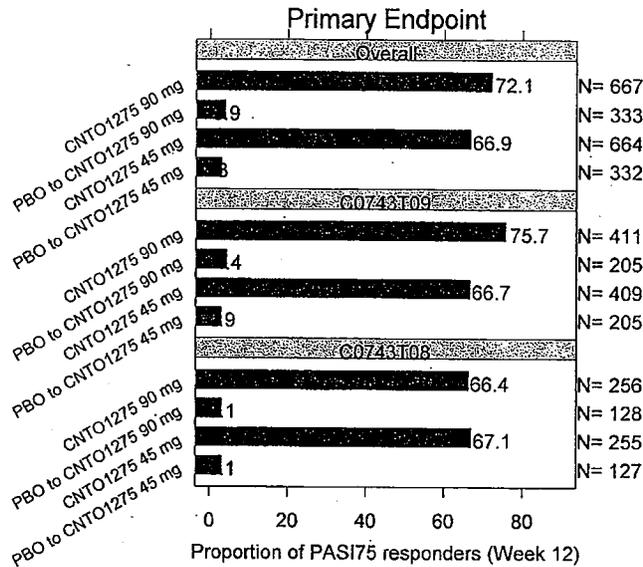
Q *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

Exposure-Response for Efficacy:

The applicant stated that the dosing regimen selected for the pivotal Phase 3 studies was based on data obtained from the Phase 2 study (C0379T04). Dosing selected for initial exposures (i.e. exposure through 12 weeks of therapy) corresponded to the middle exposures studied in Phase 2 (i.e. 90 mg and 180 mg). The frequency of dosing was based on the time to peak response (estimated to occur approximately 8-12 weeks after dosing) and the time to loss of response (generally after peak response was achieved) following initial dosing in the Phase 2 study. A q12 week maintenance was chosen as a conservative estimate of frequency of dosing. To achieve generally stable levels of exposure over time, the initial exposures (i.e. 90 mg and 180 mg) were divided into two doses spread 4 weeks apart (i.e. 45 mg or 90 mg at Weeks 0 and 4) prior to initiating q 12 week maintenance dosing.

In the Phase 3 trials (C0743T08 (Phoenix I) and C0743T09 (Phoenix II), two doses (45 mg and 90 mg) were included in both trials. The primary efficacy endpoint for PHOENIX I and II were PASI75 ($\geq 75\%$ improvement in PASI from baseline to Week 12). Both the 45 mg and 90 mg doses of ustekinumab were statistically superior to placebo for PASI75 response at Week 12 in both studies. High proportion of PASI75 responders (66.4% to 75.7% across ustekinumab groups in each study) at Week 12 was consistent with results from Phase 2. The proportion of responders on placebo treated was considerably low (3-5%) in both studies across endpoints. See Figure 2.

Figure 2: Primary efficacy (PASI75) at week 12 by study and overall. The numbers represent response rate and # of subjects in each group.



Serum ustekinumab concentrations were associated with clinical response. Subjects with higher median serum concentrations of ustekinumab generally had greater clinical responses, as measured by PASI response, than subjects with lower median serum concentrations of ustekinumab. For example, the PASI75 response rate at week 12 in 135 subjects that had undetectable serum ustekinumab concentrations was 37% as measured by PASI75. The response rate increased to 75% in subjects with median concentrations ≥ 0.9 $\mu\text{g/mL}$. See pharmacometrics review for more details.

Q *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

The major (biologically potential) safety concern for ustekinumab was carcinogenicity due to its immunosuppressive mechanism of action by blocking IL-12 and IL-23 activities. Also, there was no obvious dose dependent pattern in overall adverse events (AE), serious AEs, discontinuations due to AE or death. No apparent pattern to type of malignancies was observed through 18 months of follow up (source: Dr. Carr's advisory committee presentation). Due to the lack of obvious signals, exposure-safety analysis was not conducted. See pharmacometrics review for more details.

Q *Does this drug prolong the QT or QTc interval?*

Based on the comments provided by the QT-IRT review team, ustekinumab is not expected to prolong the QT or QTc interval. During the IND stage of ustekinumab (BBIND 9590), a consult was sent to the CDER QT Interdisciplinary Review Team (QT-IRT) on June 14th, 2007 regarding a request by Centocor, Inc to not perform a thorough QT study of CNTO 1275. QT-IRT responded to this consult on July 1st, 2008. The comments provided are inserted below:

QT-IRT Comments for Division of Dermatology and Dental Products (DDDP):

1. In our opinion, monoclonal antibodies do not need to be evaluated in a thorough clinical QT study because:
 - a. as large molecules, monoclonal antibodies cannot access the hERG pore via the intracellular side, which is the target site for most small-molecule QT-prolonging drugs; and
 - b. monoclonal antibodies can have off-target cardiac effects but QT prolongation has not been observed.

We recommend that routine ECG monitoring in clinical studies should be performed to capture any important effects. Centocor has incorporated ECG evaluation in their phase 1 and 2 studies and plans to continue ECG monitoring in phase 3 studies.

Reviewer's Comments: In the clinical trials the potential impact of CNTO 1275 on cardiovascular risk was evaluated as per the Agency's recommendation. The clinical reviewer informed this reviewer that these analyses based on these events observed over a 1-year period, did not demonstrate an impact of ustekinumab on cardiovascular risk.

b(4)

- Q Are the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issues?**

The proposed dosing recommendations for ustekinumab by the sponsor were:

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

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

The AUC-PASI75 response rate model was used to explore alternate dosing regimens, such as one dose for all (45 or 90 mg) and several weight-based dosing regimens. The aim was to derive a regimen that might yield optimal PASI75 response rate for entire population. According to the observed data as well as model predictions, a 45 mg dose is suboptimal in heavier body weight subjects and a 90 mg dose does offer higher benefit in these subjects.

The key findings from exploring alternative dosing regimen were:

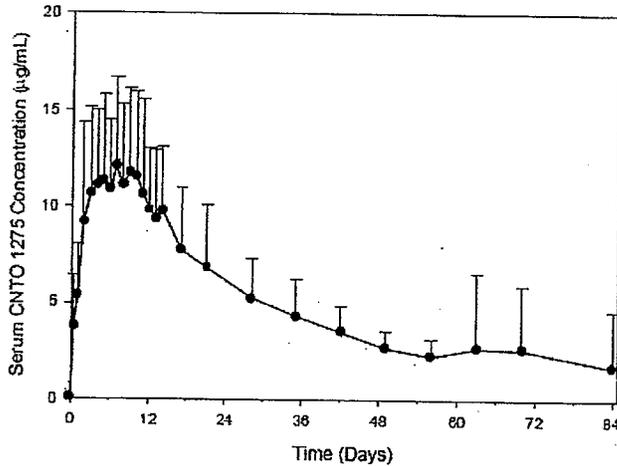
- PASI75 response rate can be further maximized by weight based adjustment.
 - Administration of ustekinumab based on two step body weight cut off (100 kg) increases the overall response rate to 70% with the gains in heavier subjects.
 - Administration of ustekinumab based on 3 step body weight cut offs (<70, ≥70-<100 and ≥100 kg) or 5 step body weight cut offs (<45, ≥45-<60, ≥60-<75, ≥75-90 and >90 kg) or semi-continuous (mg/kg) weight based dosing could yield PASI75 response rate comparable to administration of 90 mg to all subjects (overall 75%).
- None of the body weight based adjustments will yield AUCs in excess of those observed after 90 mg administration. All predictions are within the observed AUC ranges.
- In the same order the necessity of accurate dose calculation seem to increase.
- These data were presented to the advisory committee (<http://www.fda.gov/ohrms/dockets/ac/cder08.html#DermatologicOphthalmicDrugs>) on June 17, 2008, the two step dosing proposal was recommended by 7 votes vs 3 votes for three step dosing proposal.
 - The main concerns from the committee were
 - Lack of data at 67.5 mg
 - Possible delays in generating stability data for 67.5 mg
 - Lack of availability of information on the lowest effective dose

Pharmacometric Reviewer's comments: Each of the dosing strategies explored here offer different advantages. In reviewer's opinion, all the concerns above can be alleviated through objective discussions. Because the perceived benefit needs to be clinically justified, the reviewer found the discussion at advisory committee meeting useful. The open public hearing added to the gravity of psoriasis in social setting, thus maximizing responder rate should be the goal of these therapies. Based on increased benefit and lack of any exposure related safety concerns, the reviewer recommends three step dosing regimen. See pharmacometrics review for more details.

Pharmacokinetic Characteristics of Ustekinumab:

Q *What are the single dose and multiple dose PK characteristics of the drug?*

Figure 2: Mean (+SD) Ustekinumab Serum Concentrations (mcg/mL) Over Time after a Single SC Dose of 90 mg Ustekinumab to Healthy Male Volunteers



In general, ustekinumab concentrations peaked in serum between 7 and 11 days after the SC administration of a 90 mg dose to healthy volunteers, subsequently clearing from serum in an apparent mono-exponential manner.

Absorption:

In healthy subjects (C0743T11), the median T_{max} occurred approximately 8.5 days after a single 90 mg SC administration. This was comparable to the median T_{max} of 7 to 14 days) obtained in subjects with psoriasis (C037902; dose ~ 24 to 240 mg and C037904; dose = 45 mg and 90 mg) following a single SC administration of ustekinumab. Based on a cross-study comparison of data between studies C0379T01 (IV) and C0379T02 (SC), the absolute bioavailability (F) of CNTO 1275 was estimated to be 57.2% (ranging from 24.4 % to 95.0 %) following a single SC administration (0.27 mg/kg to 2.7 mg/kg, or ~ 24 to 240 mg based on a median body weight of 90 Kg in psoriasis subjects).

Table 2 Summary of Ustekinumab Absorption parameters after a single SC administration

Study Population Study ID and Dosing Regimen	Summary Statistics	C _{max} (µg/mL)	T _{max} (day)	AUC (µg·day/mL)
Subjects with Psoriasis C0379T02 0.27 mg/kg	N	5	5	5
	Mean ± SD Median	3.08 ± 1.70 2.23	13.1 ± 3.4 14.2	90.8 ± 35.8 94.1
0.675 mg/kg	N	4	4	4
	Mean ± SD	5.22 ± 2.58	11.6 ± 5.1	169.7 ± 39.4

1.35 mg/kg	Median	4.37	14.0	169.3
	N	4	4	4
	Mean ± SD	7.21 ± 2.39	10.7 ± 4.0	323.1 ± 86.7
2.7 mg/kg	Median	6.26	10.7	294
	N	4	4	4
	Mean ± SD	14.10 ± 2.82	12.3 ± 3.5	832.3 ± 390
Psoriasis Subjects C0379T04 45 mg	Median	14.65	14.0	911.3
	N	22	22	18
	Mean ± SD	2.7 ± 1.2	15.3 ± 13.5	196.7 ± 298.2
90 mg	Median	2.4	13.5	84.9
	N	24	24	21
	Mean ± SD	6.1 ± 3.6	9.9 ± 7.4	274.9 ± 206.5
Healthy Subjects C0743T11 90 mg	Median	5.3	7.0	226.9
	N	30	30	23
	Mean ± SD	15.17 ± 5.01	10.23 ± 10.41	399.81 ± 135.65
	Median	15.31	8.5	366.0

Although the T_{max} between psoriasis subjects and healthy subjects was comparable for the same dose, the C_{max} and AUC values were higher in healthy subjects compared to psoriasis subjects. In the Phase 2 psoriasis study (C0379T04), mean (SD) C_{max} and mean (SD) AUC values were 5.36.1 (3.6) µg/mL and 227 274.9 (206.5) µg·day/mL, respectively, following a single 90 mg SC dose. In the Phase 1 PK study in healthy subjects, the same dose (single 90 mg SC dose) resulted in relatively higher mean (SD) C_{max} and AUC values (15.3 15.2 (5.0) µg/mL and 366 399.8 (136) µg·day/mL, respectively). These findings of higher C_{max} and AUC in healthy subjects may be attributed to a variety of factors including differences in PK sampling schedules between the 2 studies and the, difference in weight between the 2 study populations or higher binding target concentrations (IL-12/IL-23) in psoriasis patients. Subjects in the C0379T04 psoriasis study were generally heavier (median body weight 89.0 kg; range: 51.0 kg to 220.4 kg) compared with the healthy subjects in the C0743T11 PK study (median body weight 81.3 kg; range: 61.3 kg to 94.9 kg).

Distribution:

The mean (SD) values of apparent volume of distribution at the terminal phase (V_z/F) following a single SC administration was from 72.8 (34.2) to 178.7 (85.2) mL/kg in psoriasis subjects (C0379T02 and C0379T04) and 90.21 (33.1) mL/kg in healthy subjects (C0743T11). The mean (SD) V_z values ranged from 56.1 (6.5) to 82.1 (23.6) mL/kg following a single IV administration (dose ~8.1 to 405 mg based on body weight of 90

kg) in subjects with psoriasis (C0379T01). As this represents 5.2 to 8.2 % of the body weight, this finding suggests ustekinumab is primarily confined to the vascular system with limited extravascular distribution.

Table 3 Summary of Ustekinumab distribution parameters after a single SC administration

Study Population Study ID and Dosing Regimen	Summary Statistics	Vz/F (mL/Kg)
Subjects with Psoriasis C0379T02 0.27 mg/kg	N	5
	Mean ± SD	72.8 ± 34.2
	Median	79.4
0.675 mg/kg	N	4
	Mean ± SD	106.1 ± 34.9
	Median	96.6
1.35 mg/kg	N	4
	Mean ± SD	131.1 ± 29.2
	Median	131.3
2.7 mg/kg	N	4
	Mean ± SD	144.4 ± 33.7
	Median	144.3
C0379T04 45 mg	N	18
	Mean ± SD	160.5 ± 64.5
	Median	154.2
90 mg	N	21
	Mean ± SD	178.7 ± 85.2
	Median	160.5
Healthy Subjects C0743T11 90 mg	N	23
	Mean ± SD	90.21 ± 33.08
	Median	85.77

The Vz/F in subjects with psoriasis is higher than that observed in healthy subjects. The applicant stated that the differences observed could be attributed to limited sample size in C0379T02 (n = 4 to 5 subjects per group), the differences in sampling schedules, and the inter-study and/or inter-subject variability. Subjects in the C0379T04 psoriasis study were generally heavier (median body weight 89.0 kg; range: 51.0 kg to 220.4 kg) compared with healthy subjects in the C0743T11 PK variability study (median body weight 81.3 kg; range: 61.3 kg to 94.9 kg).

Metabolism:

The exact metabolic pathway for CNTO 1275 has not been characterized. The applicant stated that as a fully human IgG1 κ mAb, CNTO 1275 is expected to be metabolized in the same manner as any other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways). These metabolic pathways are believed to result in the recycling of amino acids into non-drug related proteins/peptides. No studies on metabolites of ustekinumab have been performed and the applicant stated that they are not expected for monoclonal antibodies (ICH S6).

Elimination:

In healthy subjects, the mean (SD) terminal half-life ($t_{1/2}$) obtained after a single 90 mg dose administration (C743T11) was 22.1 (12.1) days. In psoriasis subjects, the mean (SD) terminal half-life after a single SC administration (C0379T02; dose = 24 to 240 mg and, C0379T04, dose = 45 mg and 90 mg) was from 14.9 (4.6) to 45.6 (80.2) days. The mean (SD) $t_{1/2}$ after multiple SC administrations (C0379T04) of 45 mg and 90 mg was 24.9 (7.9) days and 28.1 (7.3) days, respectively.

The mean (SD) apparent systemic clearance (CL/F) following a single SC administration of 90 mg of ustekinumab was 3.1 (1.1) mL/day/kg in healthy subjects (C0743T11). The mean (SD) CL/F following a single SC administration ranged from 3.4 (1.7) to 5.8 (3.5) mL/day/kg in psoriasis subjects (C0379T02, dose = 24 to 240 mg and, C0379T04, dose = 45 mg and 90 mg).

In psoriasis subjects, the mean (SD) terminal half-life ($t_{1/2}$) after a single SC administration (C0379T02 and C0379T04) was from 14.9 (4.6) to 45.6 (80.2) days. The mean (SD) $t_{1/2}$ after multiple SC administrations (C0379T04) of 45 mg and 90 mg was 24.9 (7.9) days and 28.1 (7.3) days, respectively. In healthy subjects, the mean (SD) $t_{1/2}$ obtained after a single 90 mg dose administration (C743T11) was 22.1 (12.1) days. The half-life was comparable between psoriasis subjects and healthy subjects.

The mean (SD) values of the apparent total systemic clearance (CL/F) following a single SC administration ranged from 3.4 (1.7) to 5.8 (3.5) mL/day/kg in psoriasis subjects (C0379T02 and C0379T04). The median (SD) CL/F following a single SC administration was 3.1 (1.1) mL/day/kg in healthy subjects (C0743T11).

Table 4 Summary of Ustekinumab elimination parameters after a single SC administration

Study Population Study ID and Dosing Regimen	Summary Statistics	Half-life ($t_{1/2}$) (day)	CL/F (mL/day/kg)
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Subjects with Psoriasis C0379T02 0.27 mg/kg	N	5	5
	Mean ± SD	14.9 ± 4.6	3.43 ± 1.65
	Median	15.2	2.68
0.675 mg/kg	N	4	4
	Mean ± SD	17.3 ± 2.5	4.20 ± 0.95
	Median	16.5	4.15
1.35 mg/kg	N	4	4
	Mean ± SD	21.2 ± 3.6	4.34 ± 0.95
	Median	22.1	4.56
2.7 mg/kg	N	4	4
	Mean ± SD	28.6 ± 9.3	4.17 ± 2.75
	Median	32.3	3.10
C0379T04 45 mg	N	18	18
	Mean ± SD	45.6 ± 80.2	5.8 ± 3.5
	Median	19.8	5.3
90 mg	N	21	21
	Mean ± SD	26.7 ± 19.3	5.7 ± 3.6
	Median	21.2	4.5
Healthy Subjects C0743T11 90 mg	N	23	23
	Mean ± SD	22.07 ± 12.10	3.11 ± 1.11
	Median	20.35	3.03

The CL/F values were higher in subjects with psoriasis compared to healthy subjects. These findings of higher CL/F values in subjects with psoriasis may be attributed to a variety of factors including differences in PK sampling schedules, inter-study and/or intersubject variability, differences in binding to the IL-12/IL-23, or differences in weight between the study populations. Subjects in the C0379T04 psoriasis study were generally heavier (median body weight 89.0 kg; range: 51.0 kg to 220.4 kg) compared with subjects with MS in C0379T03 study (median body weight 71.2 kg; range: 45.9 to 123.5 kg) and healthy subjects in the C0743T11 PK variability study (median body weight 81.3 kg; range: 61.3 kg to 94.9 kg).

Q. What are the Population Pharmacokinetic Parameters of ustekinumab?

Serum ustekinumab concentration data collected from the 2 phase 3 studies (C0743T)8 and C0743T09) were utilized to perform a population PK analysis using non-linear mixed effect modeling (NONMEM) to estimate the apparent clearance (CL/F) and apparent volume of distribution (V_z/F) of ustekinumab. The estimated population CL/F and V/F were 0.465 L/d (~5.2 mL/kg/d) and 15.7 L (~174.4 mL/kg) respectively in subjects with a

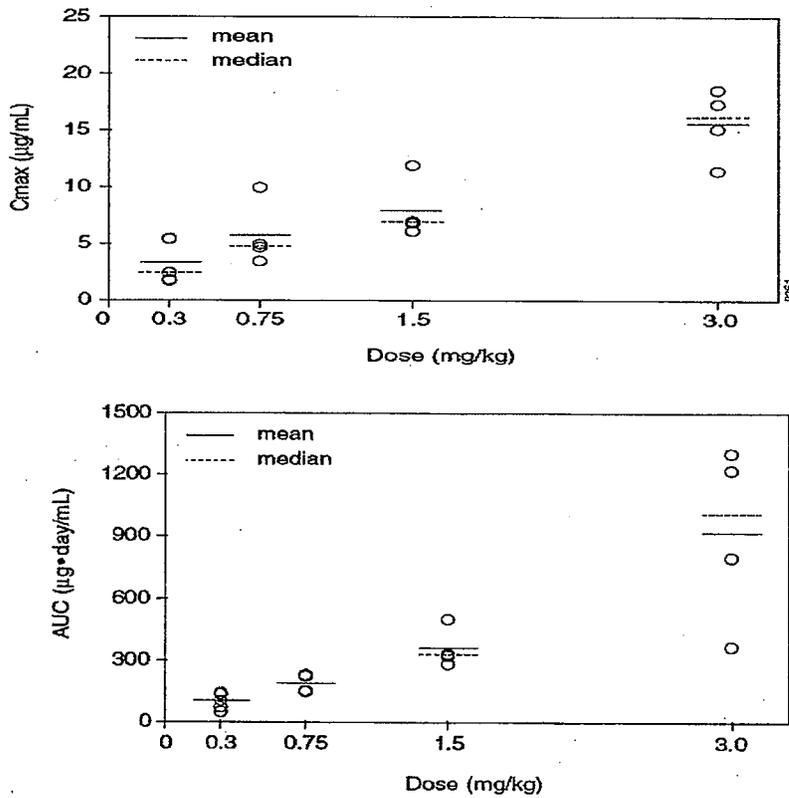
body weight of 90 kg. The median $t_{1/2}$ of ustekinumab was estimated to be 21.6 days. These findings were consistent with the values obtained with the phase 1 and 2 intense sampling data.

Q Based on the PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose Proportionality after Single- and Multiple-Dose Administration:

The C_{max} and AUC values increased in an approximately dose-proportional manner (as shown in Table 2 above) in subjects with psoriasis after a single SC administration (C0379T02) at doses ranging from 0.27 to 2.7 mg/kg (approximately 24 mg to 240 mg, based on an assumed body weight of 90 kg in psoriasis subjects). The C_{max} and AUC of CNTO 1275 were linearly correlated with the dose ($r = 0.89$ and 0.85 , respectively). The doses selected for the Phase 3 studies fell within this dose proportional range (i.e. 45 mg and 90 mg).

Figure 3 Plot of individual C_{max} ($\mu\text{g/mL}$) (upper panel) and AUC ($\mu\text{g}\cdot\text{day/mL}$) (lower panel) vs. Dose



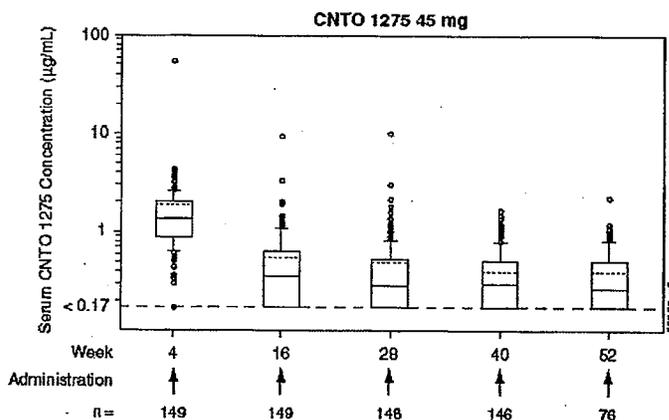
A dose-proportionality in serum CNTO 1275 concentrations was observed in each of the two Phase 3 studies (C0743T08 and C0743T09). Serum CNTO 1275 concentrations were higher in the 90 mg dose group compared to the 45 mg dose group, with differences between the two groups showing dose proportionality. The mean (SD) steady-state trough serum concentrations at Week 28 in study C0743T08 and C0743T09 was 0.3 (0.7) and 0.3 (0.3) $\mu\text{g/mL}$, respectively (45 mg every 12 weeks), and 0.6 (0.6) and 0.6 (0.6) $\mu\text{g/mL}$ respectively, (90 mg every 12 weeks).

Q How do the PK parameters change with time following chronic dosing?

The pharmacokinetics of ustekinumab after single-dose and repeated-dose administrations was evaluated in study C0379T04. This was a parallel study of single and multiple SC dose regimens with 2 fixed doses (45 mg and 90 mg). For subjects who received 4 weekly SC administrations, the median $t_{1/2}$ was approximately 21 days to 30 days, which is comparable to the $t_{1/2}$ after a single SC administration in the same study (approximately 20 days to 21 days). These results indicate that the $t_{1/2}$ remained constant after multiple dose regimens.

In the 2 Phase 3 studies in subjects with psoriasis (C0749T08 and C0749T09), steady state was achieved by Week 28 after q12w maintenance SC dosing in C0743T08.

Figure 4 Box plot of pre-injection serum CNTO 1275 concentration ($\mu\text{g/mL}$) through Week 52



Median trough serum concentrations of CNTO 1275 remained consistent at Weeks 28, 40, and 52, demonstrating that steady state was achieved by Week 28. Similar results were obtained following the administration of 90 mg SC q 12w. There was no evidence of accumulation in CNTO 1275 concentrations over time when given subcutaneously q12w.

Q *What are the between- and within-subject variability of the PK parameters in patients?*

In healthy subjects, the between subject variability for C_{max}, AUC_{inf}, CL/F and V/F was of 33.0%, 33.9%, 40.1 and 40.3 % respectively.

The population PK analysis model-predicted between subject variability for CL/F and Vz/F in psoriasis patients was 41.0 % and 33.2 %, respectively. The model predicted within subject variability was 25.6 %. These data indicate that the PK variability observed in healthy subjects were similar to those observed in psoriasis subjects.

2.3 Intrinsic Factors

Q *What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?*

The influences of intrinsic factors on the pharmacokinetics of ustekinumab were mainly evaluated as covariates in the population PK analysis.

Body Weight:

Body weight is the major intrinsic factor affecting ustekinumab exposure and response. See Pharmacometrics review for further details. The change in CL/F due to body weight was from -12% to +11% of the median CL/F estimate when body weight increased from 25 percentile (76.0 kg) to 75 percentile (103.5 kg) of the subject values. The change in V/F due to body weight was from -11% to +11% of the median Vz/F estimate when body weight increased from 25 to 75 percentile of the subject values. The comparison of CL/F and Vz/F between heavier (>100 kg) and lighter subjects (≤100 kg) is provided below. Median CL/F and V/F values were 0.44 L/d and 14.2 L, respectively, in subjects with body weight ≤100 kg; and were 0.68 L/d and 19.5 L, respectively, in subjects with body weight >100 Kg. This represents approximately 55% higher CL/F value and 37% higher Vz/F value in subjects with body weight >100 kg as compared to the respective values in subjects with body weight ≤100 kg.

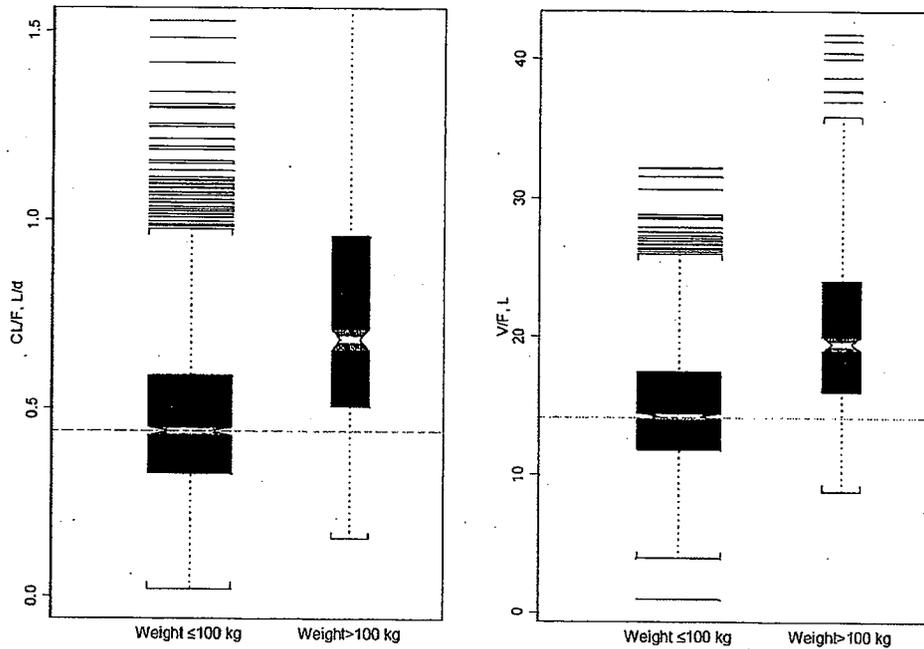


Figure 5: Source: Sponsor's figure 5.6.1 from the report pop-pk.pdf (Page 55 of 456)

Immunogenicity

It appears that immunogenicity affects the serum concentrations in one of the phase 3 trials (C0743T08). In this study, the antibody positive patients had serum concentrations that were below the limit of quantitation (LOQ) from week 12 onwards, compared to the antibody negative patients who had serum concentrations of ustekinumab above the LOQ through week 28. However, this finding was not found to be consistent in the second Phase 3 trial (C0743T09). See figures 6 and 7 below. The inconsistency appears to be due to a small number of confirmed antibody positive/negative patients in Study C0743T09 and the limitation that antibody negativity can be confirmed only when ustekinumab concentrations are not measurable.

Figure 6 Median serum ustekinumab concentrations (micrograms/mL) through Week 28 by antibody to ustekinumab status (Study C0743T08)

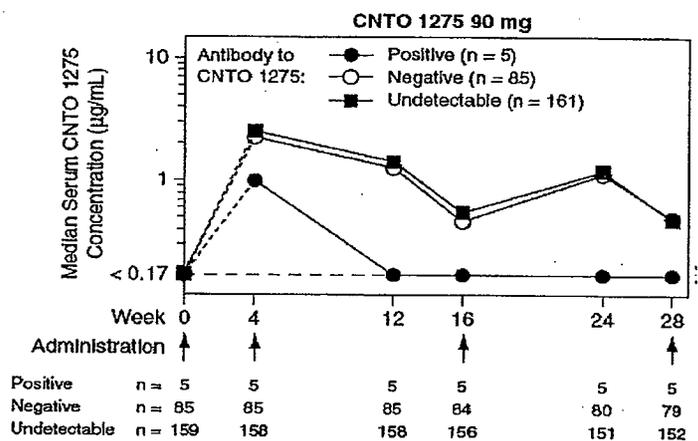
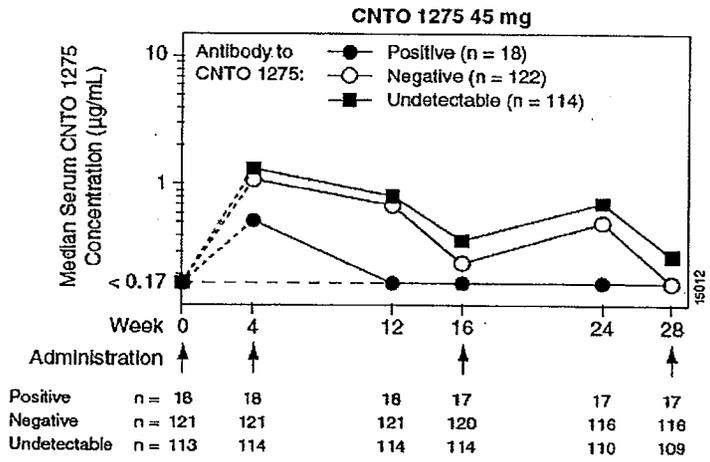
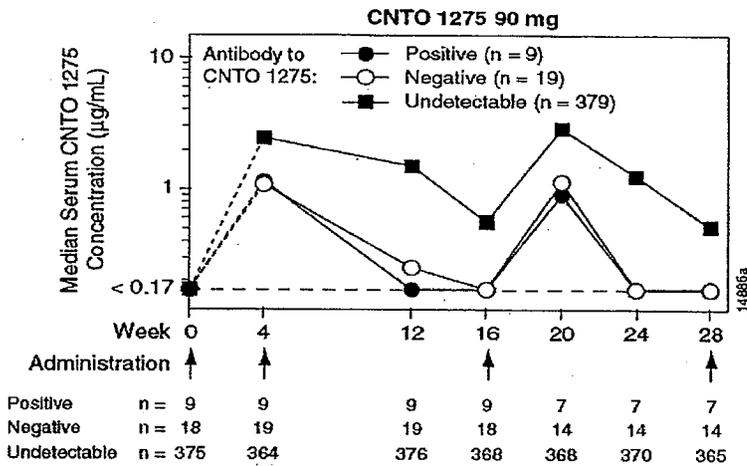
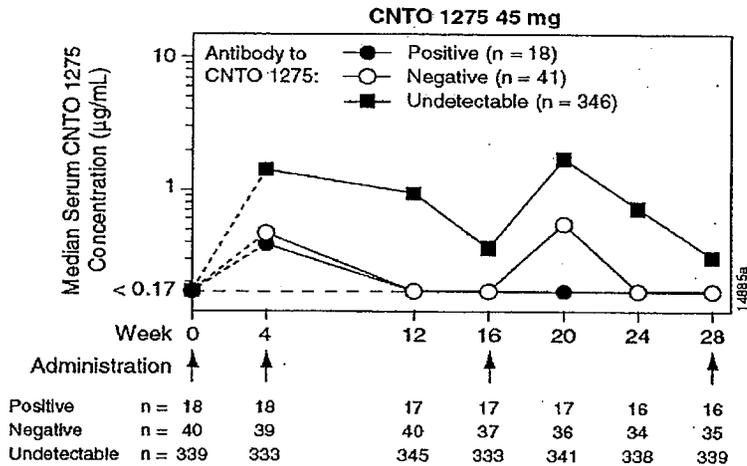


Figure 7 Median serum ustekinumab concentration (micrograms/mL) through Week 28 by antibody to ustekinumab status (Study C0743T09)



Reviewer's Comments: The applicant stated that due to the presence of serum ustekinumab concentrations that were > LOQ, subjects classified as inconclusive (undetectable) for antibodies to ustekinumab maintained median serum concentrations of ustekinumab that were consistently higher than those in subjects who were either positive or negative for antibodies to ustekinumab.

In the population PK analysis, there were 62 subjects (3%) in the combined dataset who had anti-ustekinumab antibodies over the course of treatment with ustekinumab.

The model-predicted mean CL/F value for ustekinumab was 35.5% higher in subjects with positive immune response to ustekinumab than that in subjects with other immune responses (i.e., negative or inconclusive). However, because only a small number of

subjects were determined to be positive, while the majority of patients were inconclusive in anti-ustekinumab antibody measurements in the combined dataset, the potential impact of immunogenicity on the pharmacokinetics of ustekinumab should be interpreted with caution and requires further investigation.

The immunogenicity assay method was reviewed by the product reviewer (Dr. Laurie Graham). The product reviewer reported that one important limitation of the assay used to assess for antibodies to ustekinumab is the potential for assay interference by the ustekinumab itself. Thus, a true determination of a subject's antibody to ustekinumab status can only occur after sufficient time has passed to allow a subject to clear ustekinumab ("wash-out" period). This is more of a challenge for analyzing the immune response to ustekinumab which has along half-life and continuous exposure.

The applicant stated that the concern for assay interference by ustekinumab in the immunogenicity assay has been addressed in the C0379T04 Phase 2 study, in which psoriasis subjects were administered a limited number (1 to 5 doses) of SC administrations, and then followed through 52 weeks to allow antibody assessment after an adequate wash-out period. Inserted below is a tabular summary of the immunogenicity data in the Phase 2 and 3 studies.

Table 8 Summary of incidence of antibodies to CNTO 1275 in subjects in Phase 2 and Phase 3 studies in psoriasis					
Dose Groups^a	Subjects treated	Subjects with appropriate samples^b	Status for Antibodies to CNTO 1275		
			Positive	Negative	Undetectable^c
C0379T04^d					
Overall	301	293	12 (4.1%)	250 (85.3%)	31 (10.6%)
45 mg	63	60	3 (5.0%)	53 (88.3%)	4 (6.7%)
90 mg	113	111	4 (3.6%)	96 (86.5%)	11 (9.9%)
45 mg wk x 4	63	61	3 (4.9%)	53 (86.9%)	5 (8.2%)
90 mg wk x 4	62	61	2 (3.3%)	48 (78.7%)	11 (18.0%)
C0743T08^e					
Overall	753	743	38 (5.1%)	351 (47.2%)	354 (47.6%)
45 mg dosing	378	375	24 (6.4%)	192 (51.2%)	159 (42.4%)
90 mg dosing	375	368	14 (3.8%)	159 (43.2%)	195 (53%)
C0743T09^f					
Overall	1212	1198	33 (2.8%)	90 (7.5%)	1075 (89.7%)
45 mg dosing	606	597	23 (3.9%)	57 (9.5%)	517 (86.6%)
90 mg dosing	606	601	10 (1.7%)	33 (5.5%)	558 (92.8%)
Total	2266	2234	83 (3.7%)	691 (30.9%)	1460 (65.4%)
^a Indicated dosing for C0743T08 and C0743T09 was multiple doses; dose groups include all subjects who received CNTO 1275 at any time. ^b Subjects with appropriate samples had one or more samples obtained after their first study agent administration. ^c C0379T04 used the term inconclusive. A terminology change to "undetectable" was instituted for the Phase 3 studies (C0743T08 and C0743T09) ^d Last active injection: Weeks 0-20; Last visit assessed for antibodies: Week 52 ^e Last active injection: Weeks 28-48; Last visit assessed for antibodies: Week 52 ^f Last active injection: Week 16; Last visit assessed for antibodies: Week 24					

Reviewer's Comments: Please note that the term undetectable and inconclusive were used interchangeably in the table, however, the preferred term is inconclusive.

A comparison of the data obtained in the Phase 2 and 3 studies indicates that the percentage of subjects with an inconclusive antibody status was 10.6 %, 47.6 % and 89.7 % in the Phase 2 and both of the Phase 3 studies, respectively. This data suggest that allowing time for the elimination of detectable serum ustekinumab levels in the Phase 2 study did not result in a substantially higher proportion of subjects with antibodies to ustekinumab and decrease the proportion of subjects that were inconclusive. Note that the presence of ustekinumab in serum may interfere with detectability of antibodies to ustekinumab therefore, the true incidence rate of the antibodies of ustekinumab cannot be determined from the data provided.

The low incidence of antibody-positive subjects and the high number of inconclusives precludes definitive conclusions on the impact of antibody status on the pharmacokinetics, pharmacodynamics and the clinical response of ustekinumab. The data available suggests that subjects who were positive for antibodies to CNTO 1275 tended to have lower or undetectable ustekinumab concentrations and lower clinical efficacy. The adverse events in documented antibody-positive subjects were injection site reactions (See Dr. Brenda Carr's AC presentation of June 17th, 2008). In study C0743T08, there were 3/38 (7.9%) antibody positive subjects, 11/351 (3.1%) antibody negative subjects, and 28/354 (7.9%) inconclusive antibody status subjects who had 1 or more injection site reactions through week 52. In study C0743T09, there were, 2/33 (6.1%) antibody-positive subjects, 4/90 (4.4%) antibody-negative subjects, and 28/1075 (2.6%) subjects with inconclusive antibody status to ustekinumab who had 1 or more injection site reactions through week 28. Overall, there did not appear to be an association between the development of antibodies to CNTO 1275 and the development of injection site reactions.

Reviewer's Comments: The immunogenicity data should be interpreted with caution due to the limitations of the assay method, inadequate wash-out period and the high percentage of subjects that were classified as inconclusives.

Effect of Diabetes Co-morbidity

There were 206 subjects (10.6%) with diabetes co-morbidity included in the population PK analysis. The model-predicted mean CL/F and V/F values for ustekinumab were 28.7% and 13.2%, respectively, higher in subjects with diabetes. The impact on PASI75 response of differences in ustekinumab exposure due to diabetes co-morbidity was evaluated. In the data relevant to the proposed dosing recommendations (45 mg for <100 kg subjects and 90 mg for ≥100 kg), the proportion of PASI75 responders was lower in subjects with diabetes history or existing condition. For example, 59.5% (N=37) vs 75.5% (N=421) at 45 mg for <100 Kg and 65.5% (N=29) vs 73.1% (N=193) at 90 mg for ≥100 kg. The response rate in all subgroups was at least 60%, however, the number of subjects with diabetes were much less to allow for an interpretation of precise

differences. Higher difference was seen in the 45 mg group for <100 kg subjects, the recommended 3 step dosing proposal might reduce these differences as patients with diabetes will receive 67.5 mg leading to higher ustekinumab levels. Dosing change based on diabetes co-morbidity is not recommended at this time.

Q *Based on what is known about exposure-response relationships, what dosage regimen adjustments, if any, are recommended for each subgroup listed below?*

Elderly

No dose adjustment is necessary. See Pharmacometrics review (section: Are the labeling claims based on population pharmacokinetic model acceptable?)

Pediatric Patients

According to the proposed label, the sponsor claims safety and effectiveness in pediatric patients have not been established.

Gender

No dose adjustment is necessary.

Race

No dose adjustment is necessary.

Renal Impairment

According to the proposed label, the sponsor claims no pharmacokinetic data are available in renal impairment.

The applicant stated that as a fully human IgG1 κ mAb, CNTO 1275 is expected to be metabolized in the same manner as any other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), and is subject to similar elimination. Renal excretion and hepatic enzyme-mediated metabolism are therefore unlikely to represent major elimination routes. As such, variations in renal and hepatic function are not expected to affect the elimination of ustekinumab.

Hepatic impairment

According to the proposed label, the sponsor claims no pharmacokinetic data are available in hepatic impairment.

Q *What pharmacogenetics information is there in the application and is it important or not?*

Three studies were submitted that contained gene expression data: Phase I CSR C0379T01, C0379T02 and Phase II CSR C0379T04. In addition, a publication (Toichhi et al, 2006) was also submitted to support the findings from the studies.

The key questions that were addressed during the review of these studies are as follows:

a. Are the technical aspects of the gene expression studies acceptable?

Based on the available details, the technical aspects appear to be acceptable. Some questions remain.

1. Whether any RNase inhibitor added to the biopsy sample before pulverizing it?
2. Were RIN numbers used in the QC of RNA using the Agilent bioanalyzer?
3. Why was 18S RNA used as an endogenous control in one study and GAPDH in the other studies?
4. If the PCR reactions were run in triplicate, was the data expressed as an average of all three or best two out of the three?

b. Are the findings of gene expression studies consistent across the studies?

As the Sponsor has mentioned, microarray data is definitely of exploratory nature. Thus, only TaqMan RT-PCR data will be considered for the review. Study CSR C0379T01 with 18 subjects treated with 4 different doses of CNTO 1275, showed a decrease in mRNAs for IFN γ , IL-12p40, IL-10, IL-8, TNF- α and IP-10 for all the doses examined at two weeks. It was reported in Study CSR C0379T02 that IL-12p40 mRNA levels were reduced after CNTO 1275 treatment (data not shown). In study CSR C0379T04, inconclusive results were obtained for IL-12/23 p40 mRNA levels. Based on the microarray data, different targets were selected and a decrease in mRNA levels for SERPINB3, SERPINB4, GJB2 and IL1F9 were identified in the 90mg responder group. In brief, several exploratory biomarkers in the gene expression studies have been identified, but none have been confirmed.

c. Is the sample size adequate for concluding that the expression of inflammatory cytokines and chemokines such as MCP-1, TNF- α , IP-10 and IL-8 is reduced in lesional skin biopsies?

The sample size in each dose group is very small and promising exploratory biomarkers have been identified in the studies. However, preliminary data indicates that the expression of mRNAs of inflammatory cytokines and chemokines such as MCP-1, TNF- α , IP-10 and IL-8 is reduced in lesional skin biopsies.

Q *What pharmacodynamics information is there in the application and is it important or not?*

Lesional Skin Biopsy Histology Analyses

Histological analyses were conducted in the Phase 2 psoriasis study C0379T04 to evaluate the effects of CNTO 1275 on histological measures of psoriasis including epidermal thickness and keratinocytes cell proliferation (based on an evaluation of Ki67-positive cells, a marker of cell proliferation). Punch biopsies were collected from target lesions of psoriasis subjects (N=28) at baseline and Week 12. A decrease (approx. 50 - 66 %) in the median epidermal thickness from baseline to Week 12 was observed in all CNTO treatment groups compared to the placebo group (decrease observed was approx. 5 %). The decrease in the median epidermal thickness in the combined ustekinumab treatment group at Week 12 was statistically significant (p=0.001). Only the decrease in the 45mg and 90 mg dose group were statistically significant (p< 0.05). The decrease in the 45 mg single dose group and the 90 mg single dose group were not statistically significant (p= 0.137 and 0.013, respectively).

A decrease (approx 50 - 90 %) in the number of Ki67-positive cells per field in the epidermis from baseline to Week 12 was also observed in all CNTO 1275 treatment groups compared to the placebo group (decrease observed was approx. 11 %). The decrease in the number of Ki67-positive cells per field in the epidermis from baseline to Week 12 in the combined ustekinumab treatment group at Week 12 was statistically significant (p=0.006). This decrease was statistically significant in the 45 mg multiple dose group and the 90 mg single and multiple dose groups. It was not statistically significant in the 45 mg single dose group (p=0.324).

The degree of T cell infiltration (as measured by the median number of CD3+ cells per field) was also decreased (approx. 50 - 82 %) in the psoriatic lesion biopsies of the CNTO 1275 treatment groups compared to the placebo group (decrease observed was approx. 7 %). This decrease was not found to be statistically significant (p > 0.05).

Reviewer's Comments: Therefore, while the exploratory histological analysis of the psoriatic lesions support the hypothesis that treatment with CNTO 1275 causes a reduction in the local inflammatory infiltrate in psoriatic lesions and epidermal hyperplasia, the relationship of these observations to clinical efficacy data is not well defined. Due to the inconsistency in the data obtained between dose groups and the limited information on the relationship of this analysis to the clinical outcomes, it is

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Further investigation is recommended. These findings were made with one exploratory study with a small number of subjects per dose group (N=5-7) and not adequately powered to detect a difference.

Serum Cytokine and Chemokine Analyses and T-Lymphocyte Markers:

The effect of CNTO 1275 on the levels of a limited number of serum immune mediators (chemokine/cytokine levels e.g. interferon gamma (IFN- γ), tumor necrosis factor (TNF α), interleukin-2 (IL-2)) hypothesized to be associated with psoriasis or the IL-12/IL-23 pathway was evaluated in study C0379T04. In addition, there were no apparent effects on the systemic circulating serum chemokine/cytokine concentrations following treatment with CNTO 1275. There was also no apparent effect on the major T lymphocyte populations examined after treatment with CNTO 1275.

2.4 Extrinsic Factors

Q. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?

Drug-Drug Interactions

The sponsor did not conduct in vitro metabolic-based drug-drug interaction studies using human hepatocytes or hepatic microsomes for ustekinumab.

IgG antibodies are not metabolized by CYP enzymes. Therefore, direct pharmacokinetic interactions via the CYP pathway is not expected between ustekinumab and co-administered small molecular weight drugs. The potential impact of the 28¹ most frequently used concomitant medications (including atorvastatin, metformin, acetylsalicylic acid, ibuprofen, and paracetamol) in the Phase 3 studies was evaluated using a population pharmacokinetic approach. Concomitant medications taken by fewer than or equal to 30 subjects in C0743T09 study were not included in the analysis because these were considered unlikely to provide a strong enough signal to be evaluated. Among the 28 medications selected, paracetamol (acetaminophen) (N=357), ibuprofen (N=337), acetylsalicylic acid (N=253), metformin (N=153), atorvastatin (N=140), naproxen (N=136), levothyroxine (N=119), hydrochlorothiazide (N=110) and influenza vaccine (N=106) were most commonly coadministered. None of the concomitant medications had a significant effect upon the CL/F of ustekinumab. No immunosuppressants were allowed to be used concomitantly in either study. For more details refer to pharmacometrics review- section: Appendix II: Population Pharmacokinetics Analysis.

Ustekinumab, however, might indirectly influence the expression level of CYP enzymes by antagonizing cytokine activities in psoriasis patients because cytokines are known to reduce the expression level of multiple CYP enzymes. Therefore, it is postulated that ustekinumab may increase CYP expression to baseline levels in psoriasis patients leading to decreased exposure of drugs that are metabolized by CYP enzymes. The applicant did not conduct any specific drug interaction studies to evaluate the effect of ustekinumab on CYP expression levels. The current recommendation is to ask the applicant to address this by including the suggested wording in Section 3 (labeling recommendations) based on the approved label for rilonacept (IL-1 antagonist) and the proposed label for tocilizumab (IL-6 antagonist).

¹ Acetylsalicylic Acid, Amlodipine, Amoxicillin, Atenolol, Atorvastatin, Celecoxib, Citalopram, Diphenhydramine, Hydrochlorothiazide, Hydroxyzine, Ibuprofen, Influenza Vaccine, Isoniazid, Levothyroxine, Lisinopril, Medinix, Metformin, Metoprolol, Naproxen, Omeprazole, Panadeine CO, Paracetamol, Ramipril, Salbutamol, Azithromycin, Cefalexin, Hydrocortisone, Vicodin.

2.5 General Biopharmaceutics

Drug Product Composition

Table 6: Composition of CNTO 1275 (90 mg and 45 mg) Final Vial Product (FVP)

Component	90 mg Dose Amount Per Dose (mg)	45 mg Dose Amount Per Dose (mg)	Concentration
CNTO 1275	90	45	90 mg/mL
Sucrose	76	38	██████████
L-histidine	1.0	0.5	██████████
Polysorbate 80	0.04	0.02	

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^a q.s. = Quantity sufficient, ^b NA = Not applicable

Q Was the to-be-marketed formulation the same as the pivotal clinical trial formulation (product comparability)?

Yes, the to-be-marketed formulation was used in the Phase 3 psoriasis trials (C0743T08 and C0743T09) and, a clinical pharmacology study (C0743T11) conducted in healthy volunteers.

During the clinical development of CNTO 1275, 2 sources (cell lines ██████████) of clinical material and different formulations were studied. The intended commercial formulation for SC administration by the patient or healthcare professional is the liquid formulation of ustekinumab produced by a cell line ██████████ grown in a chemically ██████████ s. However, for the Phase 1 and 2 studies (C0379T01, C0379T02 and C0379T04) the study agent was produced from cell line ██████████

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The product reviewer, Dr. Laurie Graham reviewed the product comparability of the different cell lines and formulations used in the clinical studies. The decisions on comparability was based on cumulative product quality data, and to some extent the non-clinical PK studies. No clinical PK studies were performed to assess the comparability of ustekinumab. Dr. Laurie indicated that the comparability data presented in the BLA supports comparability between all cell lines and formulations used. See product review for further details

Q What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

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

Q What bioanalytical methods were used to assess the concentrations of ustekinumab in biological fluids?

The bioanalytical methods used to determine the serum CNTO 1275 concentrations in the clinical studies were an enzyme-linked immunosorbant assay (ELISA) and an electrochemiluminescent immunoassay (ECLIA). The ELISA method was used for the Phase 1 (C0379T01 and C0379T02) and the Phase 2 (C0379T04) studies. The ECLIA method was used for the Phase 1 (C0743T11) and the Phase 3 (C0743T08 and C0743T09) studies.

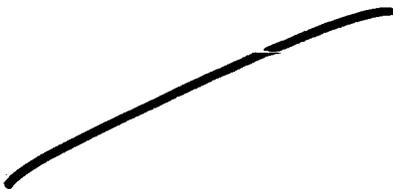
Enzyme-linked Immunosorbant Assay (ELISA) Method # CP2001V-009 for CNTO 1275 Concentration in Serum:

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Electrochemiluminescent Immunoassay (ECLIA) Method # CP2007V-001 for CNTO 1275 Concentration in Serum:

Assay Method:

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Q Were the assay methods adequately validated?

Table 7: Validation of the ELISA Bioanalytical Method:

Method	Enzyme-linked Immunosorbant Assay (ELISA)
Compound	CNTO 1275
Matrix	Human Serum
Accuracy (% Bias) <i>Intra-assay</i> <i>Inter-assay</i>	-10.2% to 2.9% -15.6 % to 1.1 %
Precision (% CV) <i>Intra-assay</i> <i>Inter-assay</i>	4.7% to 7.1 % 3.7 % to 11.3 %
Standard curve range	8.44 ng/mL to 270 ng/mL (% CV = 2.9 to 12.1 %, Accuracy = -8.9 % to 1.8 %)
Sensitivity (LOQ)	8.44 ng/mL
Specificity	Demonstrated with 3 antibodies specific for other antigens in the presence and absence of CNTO 1275. These 3 antibodies did no interfere with the detection of CNTO 1275, nor were they recognized in the CNTO 1275 assay.
Stability of CNTO 1275 in Human Serum	CNTO 1275 was demonstrated to be stable in human serum following three freeze/thaw cycles. The mean (SD) recovery after 1, 2, or 3 freeze (-70° C) – thaw (37° C) cycles was 97.3 (5.4) %, 95.6 (6.5) % and 100.2 (7.8) %, respectively. Stability@ -20° C for 40 days was also demonstrated.
Conclusion	Method validation is acceptable

Table 8: Validation of the ECLIA Bioanalytical Assay Method:

Method	Electrochemiluminescent Immunoassay (ECLIA)
Compound	CNTO 1275
Matrix	Human Serum
Accuracy (% Bias) <i>Between-Day</i>	3.3 % to 5.3 %
Precision (% CV) <i>Between-Day</i>	12.0% to 14.8 %
Standard curve range	16.88 ng/mL - 1080.00 ng/mL (%CV = 3.85 to 13.58 % and % Bias = -1.63 to 9.42)
Sensitivity (LOQ)	16.88 ng/mL (0.17 mcg/mL) (% CV=11.1% and % Bias =9.42% for N=82)

Specificity	Antibodies to CNTO 1275 were shown to compete with the reagent antibodies for binding to CNTO 1275. This may result in either lower values for the measured amount of CNTO 1275, or reduction of values below the LOQ, thereby reducing the accuracy and apparent level of detection for the method.
Recovery (Mean %)	71.8 to 140.7 % (Mean = 96.2 %) Decreased recovery (2.95% to 58.31%) of CNTO 1275 was demonstrated in immune response positive samples. The extent of the decrease in recovery directly correlated with the level of immune response as indicated by the sample titer.
Stability of CNTO 1275 in Human Serum	CNTO 1275 was demonstrated to be stable in human serum following storage @ room temperature for up to 48 hours, and @ 4° C for up to 7 weeks and -70° C for 17 months
Conclusion	Method validation is acceptable.

Brief summary of Immunogenicity Assay for CNTO 1275 (See product review for full details):

An Enzyme Immunoassay (EIA) method was validated for detection of antibodies to CNTO 1275. After blocking with assay diluent (PBS containing 1% BSA), positive (affinity purified cynomolgus monkey anti-CNTO 1275 polyclonal antibody) and negative (pooled normal human serum) controls and samples were added to immobilized CNTO 1275. Biotinylated-CNTO 1275 was added followed by streptavidin conjugated horseradish peroxidase. Plates were washed between the above steps. Tetramethylbenzidine (TMB) substrate was added, and the reaction was stopped by the addition of sulfuric acid. The optical density (OD) at 450-650 nm was determined with a spectrophotometric microplate reader. The product reviewer indicated that the method had been adequately validated however serum concentration of Ustekinumab will interfere with the immunogenicity assay.

The applicant stated that due to the interference of CNTO 1275 in this EIA, results of clinical samples were classified into 1 of 3 categories:

- Positive: a sample confirmed to contain antibodies to CNTO 1275, regardless of the presence or absence of CNTO 1275 in the sample;
- Negative: a sample without detectable antibodies to CNTO 1275 or detectable CNTO 1275 (where interference by CNTO 1275 drug was ruled out);
- Undetectable: a sample without detectable antibodies to CNTO 1275, but containing detectable levels of CNTO 1275 (i.e., possible interference by CNTO 1275).

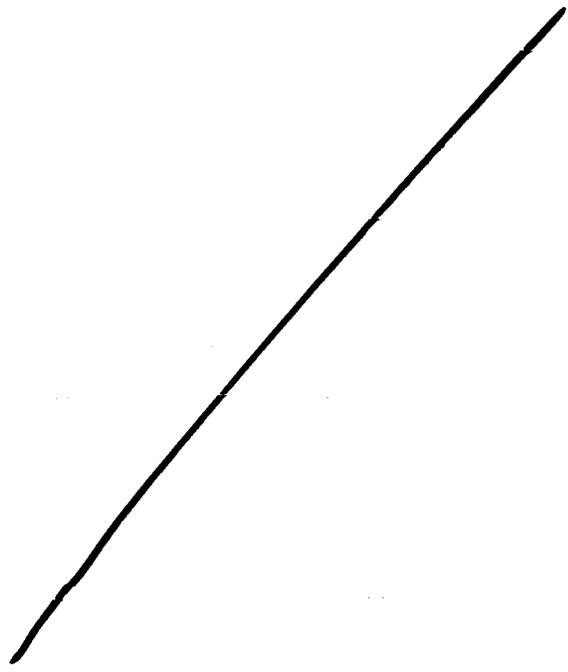
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 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)



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4.2. Individual Study Reviews

Patient PK and Initial Tolerability Study Reports

Please note that this reviewer only reviewed the pharmacokinetics and pharmacodynamics component of these study reports. Please see clinical review for detailed review of the efficacy, safety, immunogenicity and immunocompetency.

Study # C0379T01

Title of the study: A Phase I, Single Ascending Dose, Safety, Tolerability, Pharmacokinetic/Pharmacodynamic Study of the Human Monoclonal Antibody to Human IL-12 (CNTO 1275, previously referred to as 12B75) in Patients with Moderate to Severe Psoriasis Vulgaris:

Principal Investigators: Catharine L Kauffman, MD - Georgetown University Medical Center, Washington DC, USA; Alice B Gottlieb, MD, PhD - University of Medicine and Dentistry of New Jersey (UMDNJ), Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Studied Period (years): 06 April 2001 to 16 August 2002

Phase of Development: I

Objectives: The primary objectives of this Phase I, first-in-human trial were to establish the short-term safety, tolerability, and pharmacokinetic profiles of single, ascending, intravenous (IV) administrations of CNTO 1275 in subjects with moderate to severe psoriasis vulgaris.

The secondary objectives of this study were to assess the (1) immunogenicity, (2) pharmacodynamics, and (3) clinical response to single, ascending, IV administrations of CNTO 1275 in subjects with moderate to severe psoriasis vulgaris.

Methodology: This study was a Phase I, multicenter, open-label, dose-ascending, non-randomized, first-in-human trial with single IV administrations of CNTO 1275 in subjects with moderate to severe psoriasis vulgaris (plaque psoriasis). Subject cohorts were sequentially administered single doses of 0.09, 0.27, 0.9, or 4.5 mg/kg of CNTO 1275. A washout period was required for systemic psoriasis treatments, phototherapy, and topical psoriasis therapy. After up to 4 weeks of washout, subjects were enrolled in dose cohorts in an ascending dose design (doses of CNTO 1275 at 0.09 mg/kg, 0.27 mg/kg, 0.9 mg/kg or 4.5 mg/kg). Each subject received a single 2-hour IV infusion of CNTO 1275. The first subject in each dose cohort was dosed a minimum of 48 hours before subsequent subjects were dosed. Subjects remained in the clinical research unit for at least 72 hours after administration of the study drug and returned for periodic follow-up through 16 weeks post-dose.

Number of Subjects (Planned): A total of 23 subjects were planned for the study: 4 subjects at 0.09 mg/kg, 4 at 0.27 mg/kg, 5 at 0.9 mg/kg, and 5 at 4.5 mg/kg.

Diagnosis and Main Criteria for Inclusion: The study population consisted of subjects (age 18-65) with moderate to severe plaque psoriasis vulgaris involving $\geq 3\%$ body surface area (BSA) and who, in the opinion of the investigator, were in general good health. Subjects gave informed consent before study procedures were performed.

Test Product, Dose and Mode of Administration, Batch Number: Sterile liquid in glass vials containing 90 mg CNTO 1275 _____ per 10 mL vial, IV administration in doses of 0.09 (~0.1), 0.27 (~0.3), 0.9 (~1.0) or 4.5 (~5.0) mg/kg, Lot number D00PL7037. The applicant stated that the initial study design also included a 20 mg/kg dose group (n = 5). However, in consideration of continued development of CNTO 1275 only as a subcutaneously injected drug that would be injected at lower doses, the 20 mg/kg dose was removed from the protocol.

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Duration of Treatment: Single 2-hour infusion

Pharmacokinetic Sampling: During the study, subjects fasted for at least 10 hours prior to the administration of CNTO 1275 until after the 4-hour blood sample for CNTO 1275 serum concentration was obtained. Blood samples for measurement of CNTO 1275 serum concentration were obtained prior to infusion, 1 hour after the start of infusion, at the end of infusion (hour 2), and at 4, 24, 48, and 72 hours after the start of infusion of the study drug. At the 1-week, 2-week (± 1 day), 4-week (± 1 day), 8-week (± 2 days), 12-week (± 2 days), and 16-week (± 2 days) visits after study drug administration, blood samples were obtained for CNTO 1275 serum concentrations.

Bioanalytical Methods:

Serum CNTO 1275 levels were measured using a validated enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantification (LOQ) of 8.44 ng/mL.

Pharmacokinetic Analysis: The pharmacokinetic parameters (area under the concentration-time curve [AUC], observed maximum serum concentration [C_{max}], terminal half-life [t_{1/2}], t_{max}, clearance [CL], apparent volume of distribution during the terminal phase [V_z], and mean residence time [MRT]) were evaluated for each dose group.

Pharmacodynamics/Pharmacogenomics: The pharmacological effects of CNTO 1275 on IL-12 and the pathogenesis of psoriasis were evaluated by performing biological assessments on biopsied tissue from pre-specified target lesions at baseline, 48 hours, and Week 2. The biological assessments included measurement of expression of IL-12 associated cytokines. A representative biopsy target lesion, located on the trunk or extremities with adequate dermis and subcutaneous tissue, were identified by the investigator to be used for baseline and subsequent biopsy analyses. A 6-mm punch biopsy was obtained from 1 of the identified target lesions at baseline, 48 hours, and 2 weeks after administration of the study agent. The target lesion that was used for biopsy was determined by the investigator. Assessments included measurement of mRNA

expression of IL-12-associated proteins including IL-12p40, IL-12p35, IL-18, IL-8, RANTES, MCP-1, IFN γ , TNF α , IL-10 and IP-10 by quantitative real-time PCR.

Reviewer's Comments: See pharmacogenomics review of this gene expression analysis

Evaluation of Immunogenicity: The development of antibodies to CNTO 1275 was evaluated using blood samples obtained prior to infusion and at 2, 8, and 16 weeks after the infusion. Samples were allowed to clot, centrifuged, and the serum was aliquoted into storage tubes and frozen. Samples were maintained frozen during shipment from the sites to Centocor Clinical Pharmacology. The assays for CNTO 1275 serum concentration and antibodies to CNTO 1275 were performed by Centocor using a method analogous to that used in preclinical studies.

Antibodies to CNTO 1275 were determined using an antigen bridging enzyme immunoassay (EIA). Subjects were designated immune response-positive when a positive immune response in serum was detected at any timepoint following infusion. Subjects were designated as immune response-negative if they did not have a positive immune response at any time, and no detectable levels of CNTO 1275 are present following their infusion. Subjects were designated inconclusive if they did not have an immune response but detectable levels of CNTO 1275 are present at the time of the immune response assay.

Efficacy: Clinical efficacy of CNTO 1275 was monitored by performing the Physician's Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI) measurements at multiple times throughout the course of the study. In addition, the Psoriasis Severity Scale (PSS) was assessed at various times throughout the course of the study on pre-specified target lesions.

Safety: Assessment of safety for each dosing group was determined by the incidence of all adverse events (AEs), including immediate allergic reactions, and clinically significant changes from baseline in vital signs and laboratory parameters, throughout the 14-day acute safety monitoring period.

Evaluation of Immunocompetency: Because of the immunomodulatory potential of CNTO 1275, the ability of subjects to maintain a competent immune response was assessed in 2 ways: by measuring delayed type hypersensitivity (DTH) responses and polyvalent pneumococcal vaccine responses.

Statistical Methods: No interim analysis or formal hypothesis testing was conducted. Therefore, no formal sample size determination was undertaken. At each time point, all data were summarized using descriptive statistics (eg, number of observations, means, medians, standard deviations, and ranges).

Results:

Please note that this reviewer only focused on the pharmacokinetics and the pharmacodynamics data. See clinical review for the review of efficacy, safety and immunocompetency data.

Study Population

Demographics: A total of 18 subjects were enrolled and treated: 4 subjects were dosed with CNTO 1275 at 0.09 mg/kg, 4 subjects at 0.27 mg/kg, 5 subjects at 0.9 mg/kg, and 5 subjects 4.5 mg/kg. Overall, most subjects were male (78%) and Caucasian (89%). The age of the subjects ranged from 23 to 55 years. The median weight of subjects in the 0.9 mg/kg dose group (108 kg) was higher than those in the 0.09, 0.27, and 4.5 mg/kg dose groups (86, 88, and 74 kg, respectively).

		CNTO 1275				
		0.1 mg/kg	0.3 mg/kg	1.0 mg/kg	5.0 mg/kg	Total
Age (yrs.)						
Statistic						
N		4	4	5	5	18
Mean		37.5	40.0	42.8	42.8	41.0
SD		14.059	11.165	7.854	10.109	10.024
Min		23	30	32	31	23
Median		38	39	43	45	43.5
Max		51	52	54	55	55
Gender						
Category						
Male		N = 4 4 (100.0%)	N = 4 2 (50.0%)	N = 5 5 (100.0%)	N = 5 3 (60.0%)	N = 18 14 (77.8%)
Female		0 (0.0%)	2 (50.0%)	0 (0.0%)	2 (40.0%)	4 (22.2%)
Race						
Category						
Caucasian		N = 4 3 (75.0%)	N = 4 4 (100.0%)	N = 5 5 (100.0%)	N = 5 4 (80.0%)	N = 18 16 (88.9%)
Asian		1 (25.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	2 (11.1%)
Black		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Weight (kg.)						
Statistic						
N		4	4	5	5	18
Mean		95.25	93.2	99.42	84.58	92.98
SD		31.165	25.232	17.512	27.051	23.712
Min		69.1	70	68.9	65.5	65.5
Median		85.7	87.75	107.7	74	85.7
Max		140.5	127.3	110.9	131.8	140.5
Height (cm.)						
Statistic						
N		4	4	5	5	18
Mean		179.15	170.75	175.64	170.72	173.96
SD		5.7	14.407	6.982	11.035	9.755
Min		173	157	170	162	157
Median		179.8	170	174	163	174.8
Max		184	186	187	182.9	187

Baseline Disease Characteristics

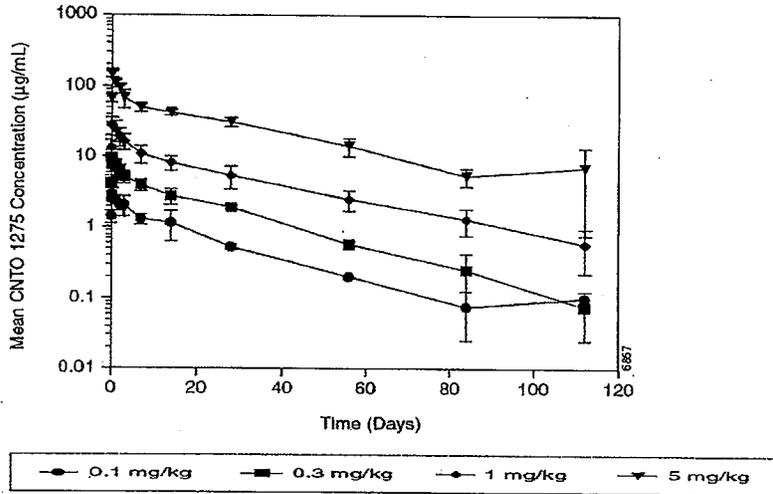
The median baseline body surface area (BSA) involvement with psoriasis varied across treatment groups (11.0% in 0.1 mg/kg, 16.5% in 0.3 mg/kg, 6.0% in 1.0 mg/kg, and 5.0% in 5.0 mg/kg). All subjects had psoriasis for more than 3 years. The median number of

years with psoriasis was comparable across treatment groups ranging from 11.8 to 15.4 years.

Pharmacokinetics/Pharmacodynamics Results:

Serum Concentrations of CNTO 1275

Figure 1: Mean (\pm SD) serum concentration-time profiles of CNTO 1275 following a single IV infusion at dose levels of 0.1, 0.3, 1.0, and 5.0 mg/kg (n = 4-5 subjects per group)



Three subjects in the 0.1 mg/kg group (1101, 1103, and 1104) had the same serum concentrations of CNTO 1275 at weeks 12 and 16 (all concentrations were 0.1 µg/mL). Two subjects in the 5.0 mg/kg group (1116 and 1118) had much higher serum concentration levels at week 16 than at week 12. Theoretically, the serum drug levels at week 16 should be much lower than week 12, and the detected drug concentrations were just around the LOQ. These serum concentrations were likely a result of bioanalytical assay variability near the LOQ. For this reason, these concentrations at week 16 were treated as outliers and excluded from the PK analyses.

Pharmacokinetic Parameters:

Table 1: Summary of ustekinumab derived pharmacokinetic parameters

CNTO 1275

	0.09 mg/kg	0.27 mg/kg	0.9 mg/kg	4.5 mg/kg
	4	4	5	5
t_{max} (day)				
Mean ± SD	0.38 ± 0.42	0.34 ± 0.44	0.11 ± 0.03	0.14 ± 0.04
Median	0.17	0.13	0.09	0.17
Range	(0.17 - 1.00)	(0.09 - 1.00)	(0.08 - 0.17)	(0.09 - 0.17)
CV%	111.0	130.5	32.2	29.7
C_{max} (µg/mL)				
Mean ± SD	2.7 ± 0.5	8.9 ± 1.6	25.5 ± 7.2	136.8 ± 17.2
Median	2.4	9.2	22.1	143.6
Range	(2.3 - 3.5)	(6.8 - 10.4)	(17.5 - 33.5)	(113.4 - 156.7)
CV%	21.5	18.2	28.3	12.6
t_{1/2} (day)				
Mean ± SD	27.0 ± 7.5	18.5 ± 3.6	25.9 ± 3.7	23.7 ± 5.7
Median	24.1	19.9	25.6	20.8
Range	(21.7 - 38.1)	(13.2 - 21.0)	(21.7 - 30.9)	(20.3 - 33.6)
CV%	27.8	19.3	14.2	24.1
AUC(0-t) (µg·day/mL)				
Mean ± SD	42.1 ± 8.4	121.9 ± 12.3	392.0 ± 110.9	1983.0 ± 234.7
Median	38.5	123.3	347.9	2073.8
Range	(36.7 - 54.5)	(105.8 - 134.9)	(276.3 - 533.5)	(1674.8 - 2262.8)
CV%	19.9	10.1	28.3	11.8
AUC (µg·day/mL)				
Mean ± SD	48.2 ± 8.0	127.6 ± 14.3	434.7 ± 133.3	2346.8 ± 359.0
Median	45.4	130.9	384.8	2485.1
Range	(42.3 - 59.9)	(107.5 - 141.2)	(306.2 - 623.5)	(1786.8 - 2682.6)
CV%	16.6	11.2	30.7	15.3
AUC/D (µg·day/mL)				
Mean ± SD	535.9 ± 89.0	472.7 ± 53.1	483.0 ± 148.1	521.5 ± 79.8
Median	503.9	484.7	427.6	552.2
Range	(470.1 - 665.7)	(398.1 - 523.0)	(340.2 - 692.8)	(397.1 - 596.1)
CV%	16.6	11.2	30.7	15.3
V_z (mL/kg)				
Mean ± SD	74.5 ± 24.1	56.1 ± 6.5	82.1 ± 23.6	66.2 ± 15.4
Median	72.6	56.6	83.2	59.59
Range	(46.9 - 105.7)	(47.8 - 63.3)	(58.2 - 118.5)	(49.2 - 87.8)
CV%	32.4	11.7	28.8	23.2
CL (mL/day/kg)				
Mean ± SD	1.90 ± 0.28	2.14 ± 0.26	2.22 ± 0.63	1.96 ± 0.34
Median	1.99	2.06	2.34	1.81
Range	(1.50 - 2.13)	(1.91 - 2.51)	(1.44 - 2.94)	(1.68 - 2.52)
CV%	14.7	12.2	28.1	17.4
MRT (day)				
Mean ± SD	35.8 ± 6.0	26.0 ± 3.2	33.5 ± 5.2	40.3 ± 11.4
Median	35.7	24.7	33.8	42.4
Range	(28.6 - 43.3)	(23.7 - 30.7)	(28.6 - 41.6)	(28.1 - 55.8)
CV%	16.8	12.2	15.6	28.4

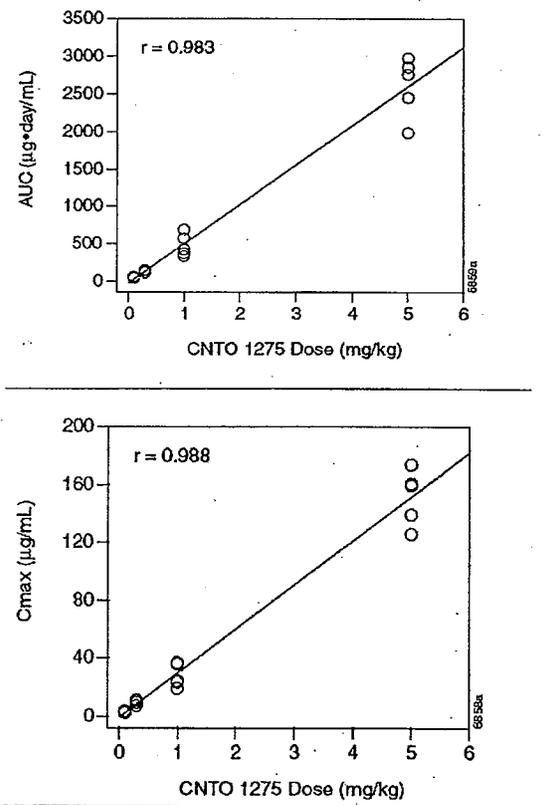
AUC/D: AUC from time zero to infinity normalized by the dose in mg/kg
 CV% = coefficient of variation (in percentage)

CNTO 1275 was slowly eliminated from the circulation and the median terminal $t_{1/2}$ values across dose levels ranged between 19.9 to 25.6 days after a single IV infusion.

Dose-Proportionality

The AUC and the C_{max} were linearly correlated with the dose. All these assessments demonstrate linear dose-independent pharmacokinetics of CNTO 1275 at the dose levels ranging from 0.09 to 4.5 mg/kg and indicate no saturation in elimination from the circulation.

Figure 2 The correlation between 1) the observed maximum CNTO 1275 concentration (C_{max}) and the dose (the upper panel); and 2) the AUC of CNTO 1275 and the dose (the lower panel) after a single IV infusion at dose levels of 0.1 - 5.0 mg/kg



Immunogenicity:

A positive immune response (i.e., the development of antibodies against CNTO 1275) was observed in 1 of 18 subjects at 16 weeks following the infusion. This immune response was specific for CNTO 1275, as characterized by complete inhibition of an immune response neutralization assay following treatment with soluble CNTO 1275 for this subject. One patient had a negative immune response to CNTO 1275. Immune response assay results in the remaining 16 subjects were inconclusive at week 16, because CNTO 1275 was present in the samples tested.

Reviewer's Comments: The sampling times for the assessment of immunogenicity did not allow for adequate wash-out period of the CNTO 1275.

Applicant's Conclusions:

CNTO 1275 is slowly eliminated from the circulation with a median terminal $t_{1/2}$ of approximately 19.9 to 25.6 days after a single IV infusion. The maximum serum concentration (C_{max}) and systemic exposure (AUC) of CNTO 1275 following a single IV infusion increased in a dose-proportional manner. The pharmacokinetics of CNTO 1275 after a single 0.1 to 5.0 mg/kg IV infusion was linear and dose-independent.

Immunogenicity of the single IV doses of CNTO 1275 used in this study was inconclusive in 16 of 18 subjects. Persistent levels of CNTO 1275 in serum interfered with the detection of antibody levels in the assay.

Reviewer's Comments: Reviewer concurs with applicants conclusions

Study # C0379T02:

Title of the Study: A Phase I, Double-blind, Placebo-controlled Study Evaluating the Safety and Pharmacology of Single Subcutaneous (SC) Administrations of Human Monoclonal Antibody to IL-12 (CNTO 1275) in Subjects with Moderate to Severe Psoriasis Vulgaris

Principal Investigators: Richard C Childers, MD - Radiant Research, Gainesville, Gainesville, FL, US; Alice B Gottlieb, MD, PhD - University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, US; Antoinette Mangione, MD, PharmD - Radiant Research, Einstein Center One, Philadelphia, PA, US

Studied Period (years): 25 Jun 2002 to 28 May 2003

Phase of Development: 1

Objectives: The primary objectives of the study were to assess the safety and pharmacokinetics of single SC administrations of CNTO 1275 in subjects with psoriasis vulgaris. The secondary objectives of the study were to assess the immunogenicity,

pharmacodynamics, and clinical response of single SC administrations of CNTO 1275 in subjects with psoriasis vulgaris.

Methodology: This was a Phase 1, multi-center, randomized, double-blind, placebo-controlled study with single SC administrations of CNTO 1275. Twenty-one subjects were randomized to active or placebo treatment within 1 of 4 sequential escalating dose cohorts (0.27 mg/kg, 0.675 mg/kg, 1.35 mg/kg, or 2.7 mg/kg) across 3 sites. The Safety Monitoring Committee completed a blinded comprehensive safety assessment on the 0.27 mg/kg and 0.675 mg/kg dose cohorts before dosing was initiated in the 1.35 mg/kg and 2.7 mg/kg dose cohorts. Each subject received a single dose of CNTO 1275 or placebo by SC injection. Subjects remained in the clinic for at least 8 hours after administration of study agent and returned for periodic follow-up visits throughout the 24-week study period.

Number of Subjects (Planned): A total of 20 subjects were planned for the study, 5 in each dose cohort. Subjects were required to have at least 4 weeks of follow-up.

Diagnosis and Main Criteria for Inclusion: Subjects (ages 18 - 65) with moderate to severe plaque psoriasis involving $\geq 3\%$ body surface area (BSA) and who, in the opinion of the investigator, were generally in good health.

Test Product, Dose, and Mode of Administration, Batch Number: Subjects received a single dose of CNTO 1275 (90 mg/mL, 0.27 mg/kg, 0.675 mg/kg, 1.35 mg/kg, or 2.7 mg/kg by SC injection. Lot number D01PJ7094.

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Duration of Treatment: Subjects participated for up to 28 weeks (i.e. 4 weeks before to 24 weeks after a single SC administration of study agent) with approximately 16 subject visits.

Reference Therapy, Dose, and Mode of Administration, Batch Number: Subjects received a single dose of placebo at a volume equivalent to the active dose volume (0.9% sodium chloride injection, United States Pharmacopeia) by SC injection.

Pharmacokinetic Sampling: Blood samples for measurement of serum CNTO 1275 concentration were obtained prior to administration of study agent and at 8, 24, 48, and 72 hours after administration of study agent. In addition, blood samples for the measurement of CNTO 1275 in the serum were obtained on day 4 and at weeks 1, 2, 4, 8, 12, 16, 20, and 24 post-dose.

Bioanalytical Method:

Serum CNTO 1275 concentrations were measured using a validated enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantification (LLOQ) of 8.44 ng/mL.

Pharmacokinetics: Serum concentrations of CNTO 1275 were summarized (mean, SD, median, and range) for each treatment group over time. PK parameters (C_{max} , t_{max} ,

AUC [0-t], AUC, AUC/D, CL/F, Vz/F, MRT, F, and $t_{1/2}$) were estimated for individuals, and summarized as mean, SD, median, and range for each treatment group. Individual serum CNTO 1275 concentrations and mean serum CNTO 1275 concentrations were plotted by treatment group and time point. Correlation of C_{max} and AUC with dose was also determined.

Pharmacodynamics:

Tissue Biopsies

A representative biopsy target lesion, located on the trunk or extremities with adequate dermis and SC tissue, was identified by the investigator to be used for biopsy analyses. A 6-mm punch biopsy was obtained from the pre-identified target lesion at baseline and 1 week after administration of the study agent. RNA was obtained from the 6-mm punch biopsy using an RNeasy® midi kit (Qiagen Inc, Valencia, CA) following tissue pulverization in a micro dismembrator (Braun, Germany). Changes in IL-12-related gene expression after study agent administration were then assessed by microarray analysis and quantitative TaqMan® PCR analysis.

Reviewer's Comments: Please see pharmacogenomics consult for a review of these studies.

Cell Surface Biomarkers

Blood samples for cellular biomarker analyses were collected prior to study agent administration, at 24 hours after study agent administration, and at weeks 2 and 12. Assays performed included whole blood staining for selected cell surface markers for CD4+ and CD8+ T-lymphocytes (CD3+CD45RA+, CD3+CD45RO+, CD3+CD4+CD45RA+, CD3+CD4+CD45RO+, CD3+CD8+CD45RA+, CD3+CD8+CD45RO+, CD3+CD69+, and CD3+CD25+). Anticoagulated whole blood was shipped by courier or express shipped directly to Centocor Clinical Pharmacology, and samples were analyzed the same day or the following day.

Cell surface expression of naïve, memory, and activation markers were examined by staining 100 μ L of whole blood with different multi-fluorochrome conjugated antibody panels, CD45RA FITC/CD45RO PE/CD3 PerCP/CD4 APC for distinguishing memory and naïve CD3+ and CD3+CD4+ subsets. Four-color antibody panel, CD45RA FITC/CD45RO PE/CD3 PerCP/CD8 APC was used for determining naïve and memory CD3+CD8+ T-lymphocyte subsets. The expression of activation markers CD69 and CD25 was measured by staining with three-color antibody panels CD4 FITC/CD69 PE/CD3 PerCP and CD4 FITC/CD25 PE/CD3 PerCP, respectively. After half-hour incubation of samples with the above antibody panels, stained samples albumin and fixed in 2% Formaldehyde. Stained and fixed samples were acquired on a BD FACSCalibur™ flow cytometer (Becton, Dickenson and Company, Franklin Lakes, NJ) and percent positive cells and antigen density (for activation markers) were determined using Cell Quest™ Pro software (Becton, Dickenson and Company, Franklin Lakes, NJ). Summary

statistics for cell surface biomarkers at baseline are presented for each treatment group. In addition, a by-subject listing of the percentage of CD3+ cells positive for each cell surface biomarker at each timepoint is presented. Mean fluorescent intensity (MFI) of CD69 and CD25 cell surface markers on CD3+ T-cells is summarized at baseline. A by-subject listing of MFI of the CD69 and CD25 markers on CD3+ cells is presented by timepoint.

Serum Biomarkers

Blood samples for serum IL-12 associated biomarker analyses were collected prior to study agent administration, at 8 and 24 hours after study agent administration, on day 3, and at weeks 1, 2, 4, 12, 20, and 24. Assays performed included serum cytokine panels reflective of Th1 (IFN- γ , IL-2, tumor necrosis factor [TNF]- α) and Type 2 T helper cell (Th2) (IL-4, IL-5, IL-10) lymphocyte subsets, and IL-12p70 and soluble intercellular adhesion molecule (sICAM).

Pharmacodynamic assessments included the following: serum biomarkers (serum cytokine panels reflective of Th1 [IFN- γ , IL-2, TNF- α] lymphocyte subsets, Th2 [IL-4, IL-5, IL-10] lymphocyte subsets, and IL-12 associated biomarkers [IL-12 and sICAM]); cellular biomarkers (cell surface markers for CD4+ and CD8+ T-lymphocytes [CD45RO, CD45RA, CD69, and CD25] and peripheral blood mononuclear cells); and tissue biopsies (for analysis of the expression of IL-12-associated proteins).

Serum cytokines and the cell adhesion biomarker concentrations were determined in either an individual ELISA format, or in a bead-based 6-cytokine multiplex assay format. The multiplexed analysis format for a given cytokine in the serum is characteristically not as accurate as an individual ELISA assay method at the lowest serum concentrations; however, any inaccuracy in the multiplex cytokine assay observed for an individual subject at baseline was also noted in repeated assays at other sample timepoints. Thus, within a given subject, serum cytokine concentrations at baseline can be compared with later sample collection time points to detect a CNTO 1275 treatment effect. A by-subject listing of all serum biomarker concentrations is provided. Summary statistics at baseline are presented for each serum biomarker and treatment group.

Evaluation of Immunogenicity: The development of antibodies to CNTO 1275 was evaluated using blood samples obtained prior to administration (baseline) and at weeks 2, 4, 8, 12, 16, 20, and 24. Each serum sample was allowed to clot, centrifuged, distributed into storage tubes, and then frozen. Antibodies to CNTO 1275 were assessed using an antigen bridging enzyme immunoassay (EIA).

Sample test results were classified into 3 immune response categories: positive, negative, or inconclusive. A sample could be classified as positive regardless of the presence or absence of detectable CNTO 1275. Samples designated as negative must have had an OD value ≤ 0.131 (cut-off value) in the screening assay, and must not have had a detectable level of CNTO 1275 in the serum (drug assay LLOQ = 0.09 $\mu\text{g/mL}$). Samples that did not exceed the cut-off value for a positive response but had detectable CNTO 1275 in the serum were designated as inconclusive.

To determine the immune response status of the subjects, additional criteria were used. Subjects were designated immune response-positive when a positive immune response in the serum was detected at any timepoint following administration of study agent. Subjects were designated as immune response-negative if they did not have a positive immune response at any time, and no detectable levels of CNTO 1275 were present in their sera samples following administration. Subjects were designated immune response-inconclusive if they did not have an immune response but detectable levels of CNTO 1275 were present in all samples following study agent administration. A summary table is provided for the incidence of positive immune responses by treatment group and by the titers of those responses.

Results:

Demographics: A total of 21 subjects were enrolled, treated, and analyzed (5 subjects were dosed with 0.27 mg/kg, 4 subjects were dosed with 0.675 mg/kg, 4 subjects were dosed with 1.35 mg/kg, 4 subjects were dosed with 2.7mg/kg, and 4 subjects were dosed with placebo).

	Placebo	CNTO 1275				Total
		0.3 mg/kg	0.75 mg/kg	1.5 mg/kg	3.0 mg/kg	
Subjects treated	4	5	4	4	4	21
Sex						
n	4	5	4	4	4	21
Male	4 (100.0%)	3 (60.0%)	2 (50.0%)	3 (75.0%)	3 (75.0%)	15 (71.4%)
Female	0 (0.0%)	2 (40.0%)	2 (50.0%)	1 (25.0%)	1 (25.0%)	6 (28.6%)
Race						
n	4	5	4	4	4	21
Caucasian	4 (100.0%)	5 (100.0%)	4 (100.0%)	3 (75.0%)	4 (100.0%)	20 (95.2%)
Black	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	1 (4.8%)
Age (yrs)						
n	4	5	4	4	4	21
Mean ± SD	41.0 ± 12.3	45.0 ± 9.0	48.0 ± 2.7	54.0 ± 10.8	51.0 ± 2.9	47.7 ± 8.9
Median	41.0	40.0	49.0	51.5	51.0	49.0
Range	(26.0, 56.0)	(38.0, 59.0)	(44.0, 50.0)	(44.0, 69.0)	(48.0, 54.0)	(26.0, 69.0)
Weight (kg)						
n	4	5	4	4	4	21
Mean ± SD	91.3 ± 10.1	96.2 ± 14.0	103.5 ± 23.7	101.7 ± 10.9	89.5 ± 7.9	96.4 ± 14.0
Median	91.2	100.2	105.3	100.7	91.6	96.6
Range	(81.8, 100.9)	(72.7, 109.5)	(74.7, 128.6)	(89.5, 115.9)	(78.2, 96.4)	(72.7, 128.6)
Height (cm)						
n	4	5	4	4	4	21
Mean ± SD	177.5 ± 1.6	170.4 ± 12.5	177.8 ± 10.8	173.7 ± 7.3	175.9 ± 15.7	174.8 ± 10.1
Median	177.8	167.6	175.3	175.4	182.9	177.8
Range	(175.3, 179.1)	(157.5, 184.2)	(167.6, 193.0)	(163.8, 180.3)	(152.4, 185.4)	(152.4, 193.0)

Please note that the doses in the table above are higher than the actual doses administered because the applicant stated that after this CSR was issued, a corrected absorptivity constant for CNTO 1275 of $1.54 \text{ (mg/mL)}^{-1} \text{ cm}^{-1}$ was derived. The concentration of 100 mg/mL of CNTO 1275 reported in this CSR was based on an absorptivity constant of $1.40 \text{ (mg/mL)}^{-1} \text{ cm}^{-1}$. Application of the corrected absorptivity constant changed the previously determined concentration of the formulation of CNTO 1275 used in this study from 100 mg/mL to 90 mg/mL. This correction adjusts the concentration of CNTO 1275 reported in this document by a factor of 0.9 and applies to all values in this CSR.

Three subjects withdrew consent from study participation: Subject 003-006 discontinued after completing the week-4 visit, Subject 003-002 discontinued after the week-12 visit, and Subject 003-004 discontinued after completing the week-16 visit. Subject 003-006 requested to discontinue the study at week 2; however, after discussions with study staff, the subject decided to try over-the-counter emollients (allowed by protocol) and remain in the study. Following 2 weeks on the over-the-counter products, this subject withdrew consent after completing the week-4 visit. Subject 003-002 initially requested to discontinue the study prior to week 4 due to aggravated psoriasis. The subject began using a topical therapy to treat his psoriasis and decided to remain in the study and be followed for safety purposes. However, he subsequently discontinued the study at week 12. Subject 003-004 was not able to complete the site visits at weeks 20 and 24 due to conflicts in scheduling around the holiday season, and thus, withdrew consent at week 16.

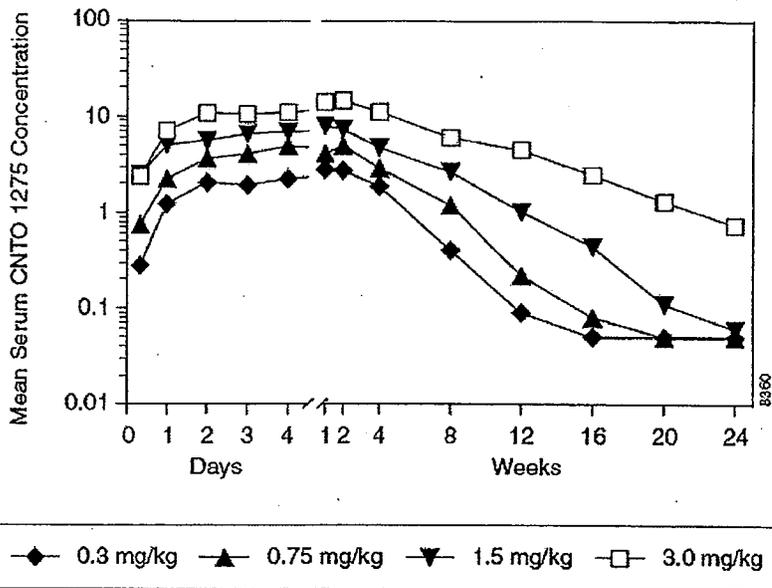
Protocol Deviations: There were 2 subjects randomized within the 3 mg/kg dose cohort (002-005 and 002-006) who received 3 syringes of study agent. This was in accordance with the Pharmacy Manual instructions not to exceed 1.35 mL per injection; however, the intent was to only administer up to 2 injections per subject. These procedures were evaluated by Centocor and considered to be acceptable since the pharmacist accurately prepared the appropriate 3 mg/kg dose based on the subjects' weights (i.e., > 93 kg). Centocor requested that adequate safety follow-up occur including evaluation of the third injection site for erythema and induration.

Pharmacokinetics:

Serum CNTO 1275 Concentrations

Results demonstrated that the mean serum concentrations of CNTO 1275 generally peaked at weeks 1 to 2 following a SC administration and then declined exponentially through weeks 12 to 24.

Figure 3 Plot of mean serum CNTO 1275 concentrations (micrograms/mL) over time for each treatment group; treated subjects



Of note, Subject 001-005 in the 0.75 mg/kg group was the only subject positive for antibodies to CNTO 1275 (at week 24). The subject's serum CNTO 1275 concentration was below the LLOQ at weeks 16 through 24, and the subject's particular CNTO 1275 concentration-time profile was similar to others in this dose group.

Pharmacokinetic Parameters

CNTO 1275 was slowly absorbed into the systemic circulation with a mean C_{max} occurring approximately 12.0 days (median 14.0 days) after a single SC administration. It was slowly eliminated from the circulation with a mean terminal t_{1/2} of approximately 20.2 days (median 17.6 days).

Table 2 Summary of derived pharmacokinetic parameters; treated subjects (Revised)

CNTO 1275

	0.27 mg/kg	0.675 mg/kg	1.35 mg/kg	2.7 mg/kg
Subjects treated	5	4	4	4
C_{max} (µg/mL)				
n	5	4	4	4
Mean ± SD	3.08 ± 1.70	5.22 ± 2.58	7.21 ± 2.39	14.10 ± 2.82
Median	2.23	4.37	6.26	14.65
Range	(1.61, 4.95)	(3.14, 9.00)	(5.54, 10.76)	(10.35, 16.76)
t_{max} (day)				
n	5	4	4	4
Mean ± SD	13.1 ± 3.4	11.6 ± 5.1	10.7 ± 4.0	12.3 ± 3.5
Median	14.2	14.0	10.7	14.0
Range	(7.1, 15.1)	(4.0, 14.3)	(7.0, 14.2)	(7.1, 14.1)
AUC (0-t) (µg · day/mL)				
n	5	4	4	4
Mean ± SD	81.7 ± 35.2	146.9 ± 37.2	250.1 ± 59.9	516.4 ± 206.7
Median	77.0	146.3	221.5	523.4
Range	(42.4, 126.1)	(107.9, 186.9)	(217.5, 340.0)	(292.0, 726.7)
AUC (µg · day/mL)				
n	5	4	4	4
Mean ± SD	90.8 ± 35.8	169.7 ± 39.4	323.1 ± 86.7	832.3 ± 390.0
Median	94.1	169.3	294.0	911.3
Range	(44.9, 129.0)	(133.5, 206.4)	(254.4, 450.0)	(330.2, 1176.5)
AUC/D ((µg · day/mL)/(mg/kg))				
n	5	4	4	4
Mean ± SD	341.4 ± 133.6	247.7 ± 55.7	240.8 ± 63.3	308.7 ± 144.9
Median	373.7	249.0	219.4	337.6
Range	(166.4, 477.7)	(195.1, 297.7)	(191.0, 333.3)	(122.3, 437.2)
t_{1/2} (day)				
n	5	4	4	4
Mean ± SD	14.9 ± 4.6	17.3 ± 2.5	21.2 ± 3.6	28.6 ± 9.3
Median	15.2	16.5	22.1	32.3
Range	(9.0, 20.6)	(15.4, 20.8)	(16.1, 24.5)	(14.8, 35.0)
CL/F (mL/day/kg)				
n	5	4	4	4
Mean ± SD	3.43 ± 1.65	4.20 ± 0.95	4.34 ± 0.95	4.17 ± 2.75
Median	2.68	4.15	4.56	3.10
Range	(2.09, 6.01)	(3.36, 5.13)	(3.00, 5.24)	(2.29, 8.18)
V_z/F (mL/kg)				
n	5	4	4	4
Mean ± SD	72.8 ± 34.2	106.1 ± 34.9	131.1 ± 29.2	144.4 ± 33.7
Median	79.4	96.6	131.3	144.3
Range	(27.2, 104.9)	(77.0, 154.2)	(96.3, 165.4)	(114.7, 174.2)

MRT (day)				
n	5	4	4	4
Mean ± SD	27.9 ± 6.4	30.3 ± 5.6	37.6 ± 4.8	51.3 ± 15.2
Median	27.0	30.5	39.2	57.8
Range	(20.2, 35.5)	(24.8, 35.6)	(30.6, 41.3)	(28.6, 61.0)
F (%)				
n	5	4	4	4
Mean ± SD	67.9 ± 26.6	49.3 ± 11.1	47.9 ± 12.6	61.4 ± 28.8
Median	74.3	49.5	43.6	67.1
Range	(33.1, 95.0)	(38.8, 59.2)	(38.0, 66.3)	(24.3, 86.9)

Dose Proportionality

The pharmacokinetics of CNTO 1275 (C_{max} and AUC) following a single 0.27 mg/kg to 2.7 mg/kg SC administration increased in an approximately dose proportional manner. The C_{max} and AUC of CNTO 1275 were linearly correlated with the dose ($r = 0.891$ and 0.852 , respectively). A 10-fold increase in dose resulted in an approximately 9.2-fold increase in mean AUC, indicating that the AUC increased in an approximate dose-proportional manner. CL/F appeared to be dose-independent (mean CL/F values were 3.4, 4.2, 4.3, and 4.2 mL/day/kg at the doses of 0.3, 0.75, 1.5, and 3.0 mg/kg, respectively). However, the terminal $t_{1/2}$ values appeared to be shorter in subjects treated with lower doses compared with subjects treated with higher doses (mean $t_{1/2}$ values were 14.9, 17.3, 21.2, and 28.6 days at the doses of 0.3, 0.75, 1.5, and 3.0 mg/kg, respectively), indicating that the mean terminal $t_{1/2}$ increases in a slight dose-dependent manner. The terminal portion of the serum concentration-time profile was not sufficient to fully characterize the $t_{1/2}$ in the lower-dose treatment groups.

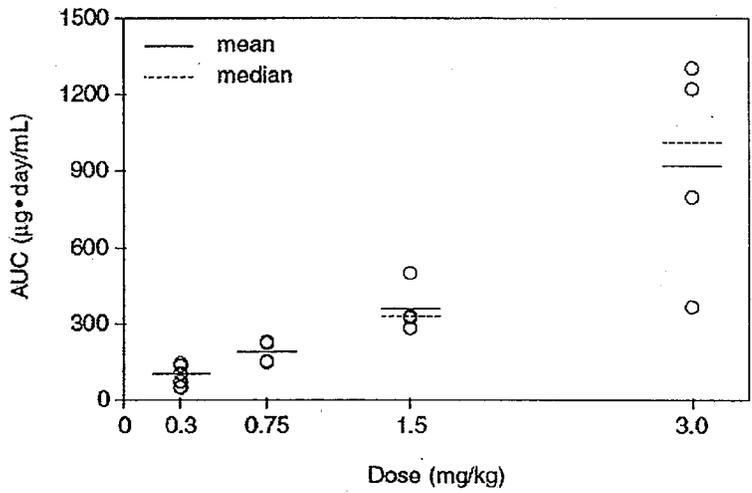
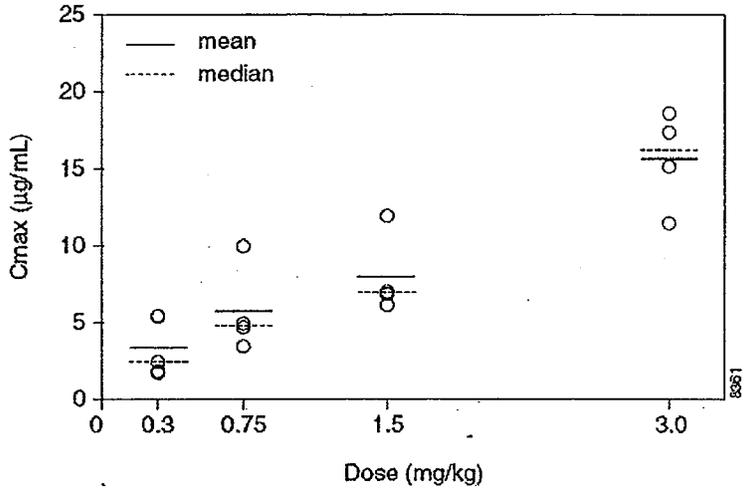
Absolute Bioavailability

Compared with Centocor study C0379T01, where the subjects were treated with CNTO 1275 as a single IV infusion (0.1 mg/kg to 5.0 mg/kg), the bioavailability (F) of CNTO 1275 following a single SC administration (0.3 mg/kg to 3.0 mg/kg) was approximately 57.2% (ranging from 24.3% to 95.0%).

Distribution

Applying this F factor, the mean apparent volume of distribution during the terminal phase (V_z) was calculated as 63.6 mL/kg, suggesting that CNTO 1275 primarily occupies the vascular space.

Figure 4 Plot of individual C_{max} (µg/mL) and AUC (micrograms·day/mL) vs. treatment group; treated subjects



(NOTE: Cmax (µg/mL), AUC, and dose values have NOT been changed to reflect concentration corrections based on absorptivity constant differences)

Pharmacodynamics Results: See pharmacogenomics review

Immunogenicity

Immunogenicity assay results were negative in 11 of 17 (64.7 %) subjects and inconclusive in an additional 5 subjects (29.4 %) because persistent CNTO 1275 levels interfered with the detection of antibody levels in the assay. One subject (5.9%) was

positive for antibodies to CNTO 1275 (positive-immune response) at 24 weeks following a single SC administration (0.75 mg/kg).

Conclusion:

PK analysis demonstrated that CNTO 1275 was slowly absorbed into the systemic circulation (C_{max} occurring approximately 12 days) and was slowly eliminated from the circulation (t_{1/2} approximately 20 days) after a single SC administration. The pharmacokinetics of CNTO 1275 (C_{max} and AUC) following a single 0.27 mg/kg to 2.7 mg/kg SC dose increased in an approximately dose proportional manner. The absolute bioavailability of CNTO 1275 following a single SC administration was approximately 57.2%.

In general, no effect of CNTO 1275 treatment was observed on T-lymphocytes and selected serum biomarkers reflective of lymphocyte activation. Treatment with CNTO 1275 was not associated with detectable changes in CD4+ or CD8+ T-lymphocyte populations of naive or memory phenotypes, and did not affect the expression of the cell activation markers CD25 and CD69. Low cytokine serum concentrations limited detection of a treatment difference. Serum sICAM concentrations were not affected by CNTO 1275 treatment.

Immunogenicity assay results were positive in 1 subject and negative or inconclusive in 16 of 17 subjects.

Reviewer's Comments: Pharmacodynamics assessments were exploratory with limitations in the study design and thus conclusions should be interpreted with caution.

Study # C0379T04:

This reviewer will only be reviewing the PK and PD component of this protocol. The clinical reviewer (Dr. B. Carr) is currently reviewing the efficacy, safety and immunogenicity component of the study report.

Title of the Study: A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel Study of Single and Multiple Dose Regimens with Subcutaneous CNTO 1275 (Human Monoclonal Antibody to IL-12) in Subjects with Moderate to Severe Psoriasis

Principal/Coordinating Investigator: Gerald Krueger, MD, University of Utah Health, Department of Dermatology, School of Medicine, Salt Lake City, Utah

Study Centers: 46 investigative sites: 28 in the US, 12 in Canada, 4 in Germany, and 2 in Belgium.

Studied Period: 25 Jun 2003/09 Mar 2005

Phase of Development: 2

Objectives: The primary objectives were (1) to evaluate the clinical response to initial single and multiple (weekly \times 4) subcutaneous (SC) injections of CNTO 1275 in order to select an induction regimen for subjects with psoriasis and (2) to assess the safety of single and multiple SC injections of CNTO 1275 in subjects with psoriasis by evaluation of adverse events (AEs) and laboratory parameters. Secondary objectives were (1) to evaluate the durability of clinical response; (2) to evaluate the efficacy of retreatment with a single SC injection (45 or 90 mg) of CNTO 1275 at Week 16 in the subgroup of subjects with Physician's Global Assessment (PGA) \geq 3; (3) to determine the pharmacokinetics of SC administered CNTO 1275 and the relationship of pharmacokinetic (PK) parameters and pharmacodynamics (PASI score); (4) to assess the pharmacodynamics of single and multiple SC injections of CNTO 1275 by measurement of relevant biomarkers; and (5) to determine the immune response to CNTO 1275 by assessment of the presence of antibodies to CNTO 1275.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled study of 2 fixed doses of SC CNTO 1275.

Number of Subjects (Planned): Approximately 300 subjects were to be randomly assigned at baseline to 1 of the 5 groups, (60 subjects per group).

Diagnosis and Main Criteria for Inclusion: Men and women 18 years of age or older who had a diagnosis of plaque-type psoriasis for 6 or more months, \geq 10% total body surface area (BSA), a baseline PASI score \geq 12, and were considered by the investigator to be candidates for phototherapy or systemic therapy.

Test Product and Reference Product, Dose and Mode of Administration, Batch Number: 45 or 90 mg CNTO 1275 was administered by SC injection. Subjects were randomized at baseline to 1 of 5 treatment groups:

- Placebo at Weeks 0, 1, 2, 3 and 16,
- 45 mg single dose CNTO 1275 at Week 0 and placebo at Weeks 1, 2, and 3;
- 90 mg single dose CNTO 1275 at Week 0 and placebo at Weeks 1, 2, and 3;
- 45 mg weekly \times 4 CNTO 1275 at Weeks 0, 1, 2, and 3;
- 90 mg weekly \times 4 CNTO 1275 at Weeks 0, 1, 2, and 3.

At Week 16, subjects in the CNTO 1275 groups who scored \geq 3 on PGA of psoriasis were to be retreated with 1 additional dose of CNTO 1275 at the original level (45 or 90 mg), while those with PGA $<$ 3 were to receive placebo. At Week 20, all subjects randomized to the placebo group were to receive a single dose of 90 mg CNTO 1275, subjects in the CNTO 1275 groups received placebo. One lot of CNTO 1275 (D02PJ7192) was used in this study. One lot of placebo (D02PJ7192) was used in this study

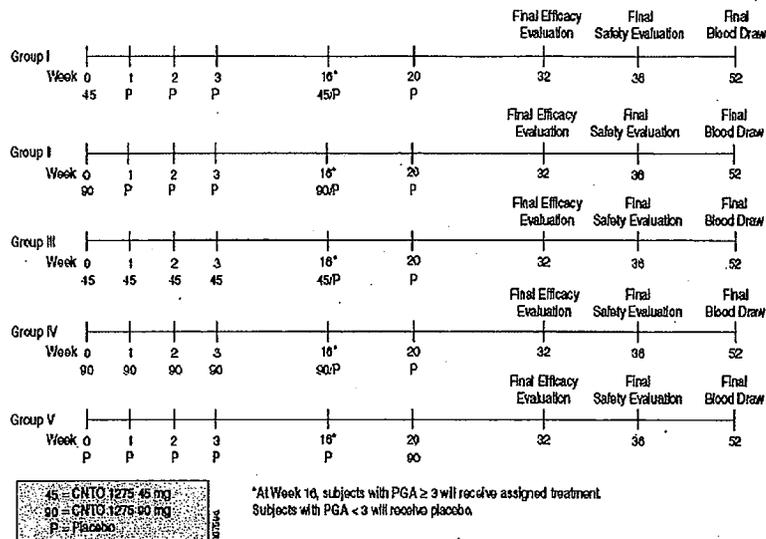


Figure 5 Dosing Scheme

Duration of Treatment: 20 weeks of treatment; efficacy data evaluated through Week 32, safety evaluated through Week 36, serum samples were obtained for PK analysis through Week 36; and serum samples were obtained for analysis of antibodies to CNTO 1275 through Week 52.

Efficacy: The primary efficacy endpoint was the proportion of subjects who achieved $\geq 75\%$ improvement in PASI from baseline (PASI 75 responders) at Week 12.

Major secondary endpoints included:

- The proportion of subjects who were PASI 75 responders through Week 32 (durability of response).
- The proportion of subjects who were PASI 75 responders after Week 16 in the subgroup of subjects with $PGA \geq 3$ (efficacy of retreatment).
- Immune response as assessed by antibodies to CNTO 1275.

Concomitant Medications for the Treatment of Psoriasis

All topical therapies that could affect psoriasis or the PASI evaluation, such as corticosteroids, tar, anthralin, calcipotriene, tazarotene, or methoxsalen, were prohibited during the study and were to have been discontinued 2 weeks prior to randomization. The only allowed concomitant treatments for psoriasis were shampoos (containing tar or salicylic acid only) and topical moisturizers. Subjects were not to use these topical agents on the morning of a study visit. Nonmedicated shampoos may have been used on the day of a visit. Concurrent use of any systemic therapy that could have affected psoriasis or the

PASI evaluation was not permitted during the study. Use of systemic antipsoriatic therapies must have been discontinued at least 4 weeks prior to randomization.

Pharmacokinetic Sampling: The pharmacokinetics of CNTO 1275 was assessed from serum CNTO 1275 concentrations through Week 36 for a subset of subjects. Serum samples were drawn on Days 1 (Week 0), 4, 8 (Week 1), 11, 15 (Week 2), 18, 22 (Week 3), 25, 36 (Week 5), 57 (Week 8), 85 (Week 12), 113 (Week 16), 116, 120 (Week 17), 141 (Week 20), 169 (Week 24), 197 (Week 28), 225 (Week 32), and 253 (Week 36). On days when the study agent was administered, samples were taken immediately before the injection.

Bioanalytical Methods: Serum CNTO 1275 concentrations were measured using a validated ELISA with a LLOQ of 0.08 µg/mL following a 1:10 dilution

Pharmacokinetics Analysis: The pharmacokinetics of CNTO 1275 was assessed from serum CNTO 1275 concentrations through Week 36 for a subset of subjects. Serum CNTO 1275 concentration was summarized by treatment group and visit using descriptive summary statistics. These summaries excluded data collected after the subject: 1) discontinued study medication; 2) skipped an injection; 3) received an incomplete injection; 4) received an incorrect injection; and/or 5) received an additional injection. PK parameter estimates were summarized by dose group. The summary of derived PK parameters excluded data collected from subjects who had: 1) insufficient blood sample collection; 2) incomplete dosing; and/or 3) poorly characterized terminal elimination phase (defined as $R^2 < 0.90$).

Pharmacodynamic Evaluation: Whole blood, serum, and tissue biopsies from pre-specified target lesions were collected for pharmacodynamic (PD) assessments of relevant cell surface markers associated with the pathogenesis of psoriasis, production of Th1/Th2 type cytokines, and the distribution and activation of cell populations associated with psoriasis pathology.

Cellular Biomarkers

Peripheral whole blood samples were to be taken from a subset of approximately 35 subjects at Weeks 0 (baseline) and prior to study administration at Week 12. Production of cytokines representative of Th1/Th2 type (IFN γ and IL-5, respectively) in response to polyclonal activators (phorbol 12-myristate 13-acetate [PMA]+ionomycin, phytohemagglutinin-P [PHA-P], and staphylococcal enterotoxin B [SEB]) was evaluated by ELISPOT technology using ImmunoSpot Analyzer Series I (Cellular Technology Limited, Cleveland, OH).

Cell surface markers associated with the pathogenesis of psoriasis were examined by staining 100 µL of blood sample with different multicolor conjugated antibody panels. Stained and fixed samples were acquired on a BD FACSCalibur flow cytometer, and percentage of positive T lymphocytes expressing these markers was determined using Cell Quest Pro software (BD Biosciences, San Diego, CA).

Whole blood staining was used to assess the following cellular biomarkers: CLA, CD25, HLADR, CXCR3, CD45RA, CD45RO, CD3+CD45RA+, CD3+CD4+CD45RA+, CD3+CD45RO+, CD3+CD4+CD45RO+, CD3+CD25+, CD3+CD4+CD25+, CD3+CD8+CD25+, CD3+HLADR+, CD3+CD4+HLADR+, CD3+CD8+HLADR+, CD3+CLA+, CD3+CXCR3+, CD3+CD4+CXCR3+, and CD3+CD45RO+CXCR3+.

Serum-based Biomarkers

Serum samples were collected at Weeks 0, 2, 12, and 32 and evaluated for cytokine levels, such as those reflective of Th1 and Th2 lymphocyte subsets and IL-12 associated biomarkers (i.e., IL-12 and soluble intercellular adhesion molecule-1 [sICAM-1]).

Biopsy Study

Investigators at selected sites identified a representative biopsy site target lesion, located on the trunk or extremities and having adequate dermis and subcutaneous tissue to be used for baseline and follow-up biopsy analyses. Two 4-mm punch biopsies were obtained from identified target lesions at Week 0 and Week 12. One biopsy was formalin-fixed for analysis by immunohistochemical methods for the distribution and activation state of cell populations associated with psoriasis pathology (eg, CD3, CD4, CD8, CD25, and CLA). The second biopsy was collected to support mRNA expression analysis.

Reviewer's Comments: See pharmacogenomics review for further details on the design of the study and the results obtained.

Antibodies to CNTO 1275: Blood samples were collected at Weeks 0, 16, 20, 24, 32, 36, and 52 and assessed for the presence of antibodies to CNTO 1275 to determine the immunogenicity of single and weekly \times 4 SC administrations of CNTO 1275. Serum was to be collected from all subjects participating in the study. A subject was considered to have developed a positive immune response if the assay result showed a significant increase following study agent injection, provided the increased reactivity could be demonstrated to bind CNTO 1275 specifically.

Because the presence of CNTO 1275 can interfere with the detection or interpretation of an antibody response, samples evaluated for antibodies to CNTO 1275 were also analyzed for CNTO 1275 concentration. Any detectable CNTO 1275 antibody responses were classified as positive, regardless of the presence or absence of CNTO 1275 in the sample. If CNTO 1275 was not detected in at least 1 sample following the last injection, and the antibody response results were negative, then the subject was classified as not having antibodies to CNTO 1275. If the antibody to CNTO 1275 results were negative, but measurable concentrations of CNTO 1275 were present in all serum samples evaluated following the final injection, the antibody status was classified as inconclusive.

The percentage of subjects developing antibodies to CNTO 1275 was summarized through Week 16, 24, 36 and 52 by dose group for subjects treated with CNTO 1275.

Results

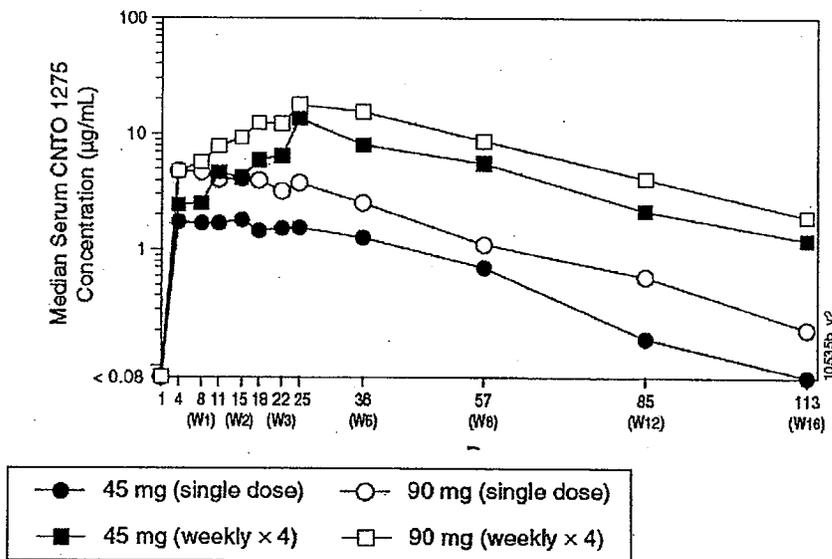
Study Population: 320 subjects were randomized to treatment and analyzed for efficacy; 319 subjects received study agent and were analyzed for safety; and 110 subjects had serum samples analyzed for pharmacokinetics of CNTO 1275. Baseline disease characteristics indicated a population of subjects with moderate to severe psoriasis with a median BSA of 21.0% (ranging from 10.0% to 92.0%) and a median PASI score of 16.4 (ranging from 12.0 to 51.0). Approximately twice as many men (69.4%) as women participated in the study, and most subjects were Caucasian (92.8%). The median age was 45 years, and the median weight was 89.0kg.

Pharmacokinetics Results:

Serum Concentration vs. time

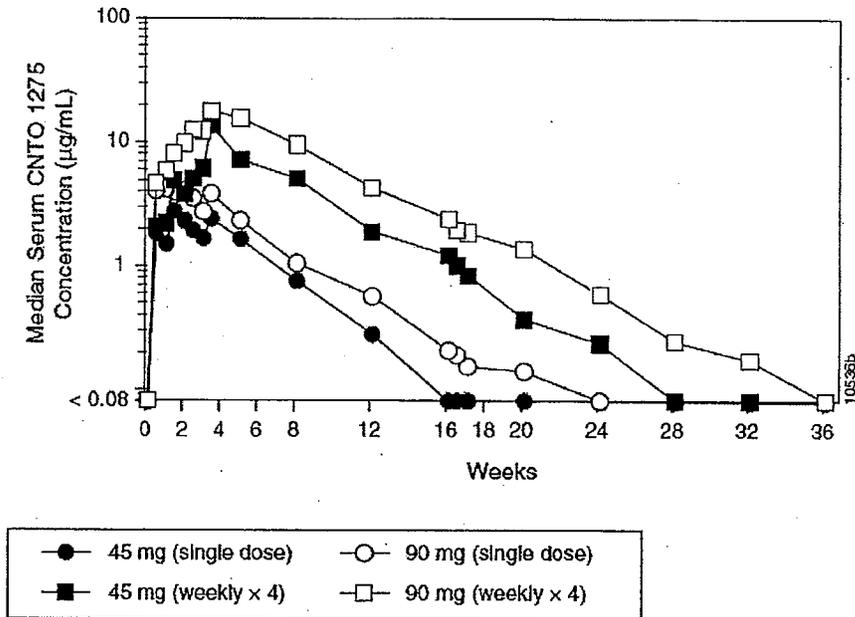
Serum concentration data were available from 110 subjects through Week 36. The median serum concentrations of CNTO 1275 generally peaked from Day 4 to Day 15 (Week 2) following a single SC administration (Week 0, Day 1), and then declined exponentially through Week 16 (45 mg single dose) to Week 24 (90 mg single dose).

Figure 6 Median serum CNTO 1275 concentration through Week 16 by visit; treated subjects



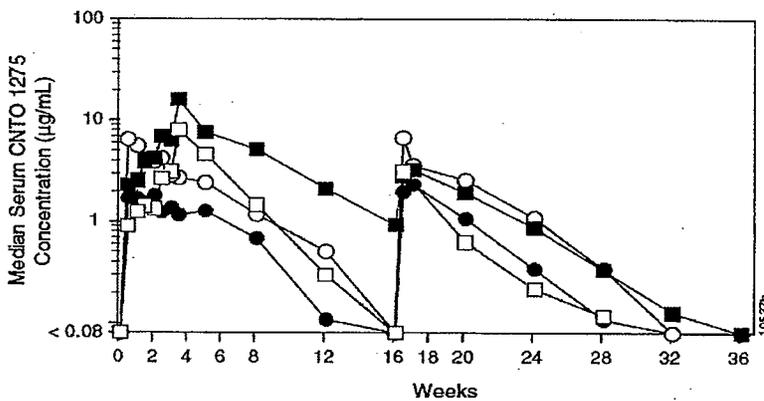
Results are shown for samples collected at Week 0, Day 4, Week 1, Day 11, Week 2, Day 18, Week 3, Day 25, Week 5, Week 8, Week 12 and Week 16 for CNTO 1275 treatment groups: 45 mg single dose, 90 mg single dose, 45 mg weekly x 4, and 90 mg weekly x 4.

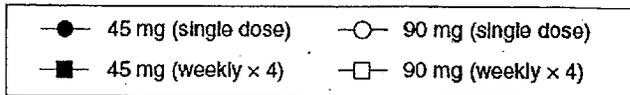
Figure 7 Median serum CNTO 1275 concentration through Week 36 by visit; subjects treated with placebo at Week 16



Results are shown for samples collected at Week 0, Day 4, Week 1, Day 11, Week 2, Day 18, Week 3, Day 25, Week 5, Week 8, Week 12, Week 16, Week 16 + 3 days, Week 17, Week 20, Week 24, Week 28, Week 32, and Week 36 for CNTO 1275 treatment groups: 45 mg single dose, 90 mg single dose, 45 mg weekly x 4, and 90 mg weekly x 4.

Figure 8 Median serum CNTO 1275 concentration through Week 36 by visit; subjects treated with CNTO 1275 at Week 16





Results are shown for samples collected at Week 0, Day 4, Week 1, Day 11, Week 2, Day 18, Week 3, Day 25, Week 5, Week 8, Week 12, Week 16, Week 16 + 3 days, Week 17, Week 20, Week 24, Week 28, Week 32, and Week 36 for CNTO 1275 treatment groups: 45 mg single dose 90 mg single dose, 45 mg weekly × 4, and 90 mg weekly × 4.

In the multiple dose groups, Subject 020-004 (45 mg) and Subjects 001-017 and 002-011 (90 mg) were actually treated with only 1 dose of CNTO 1275, and Subject 003-006 (90 mg) was actually treated with only 2 doses of CNTO 1275. Other subjects (23 in the 45 mg weekly × 4 group and 20 in the 90 mg weekly × 4 group) were treated with 4 doses of CNTO 1275 at Weeks 0, 1, 2, and 3.

In the 45 mg single dose, 90 mg single dose, and 45 mg weekly × 4 groups, the median serum concentration-time profiles of CNTO 1275 from Weeks 0 to 16 were generally similar among subjects with PGA scores < 3 who received placebo at Week 16, and subjects with PGA scores ≥ 3 who were retreated with CNTO 1275 at Week 16. This assessment could not be estimated for the 90 mg weekly × 4 groups since only 1 subject had PGA ≥ 3 and was retreated with CNTO 1275 at Week 16.

For subjects who were treated with a single dose of CNTO 1275 at Week 0 and retreated with CNTO 1275 at Week 16 (PGA ≥ 3 at Week 16), the median serum CNTO 1275 concentrations were observed to be < 0.08 µg/mL at Week 16 in both the 45 mg single dose and 90 mg single dose groups. The median serum CNTO 1275 concentrations at Weeks 24, 28, and 32 were observed to be 0.3 µg/mL, 0.1 µg/mL, and < 0.08 µg/mL, respectively, for the 45 mg single dose group, and 1.1 µg/mL, 0.3 µg/mL, and < 0.08 µg/mL, respectively, for the 90 mg single dose group. These levels were generally similar to those levels observed at the equivalent timepoints after the first dose (median serum CNTO 1275 concentrations were observed to be 0.7 µg/mL, 0.1 µg/mL, and < 0.08 µg/mL at Weeks 8, 12, and 16, respectively, for the 45 mg single dose group, and 1.2 µg/mL, 0.5 µg/mL, and < 0.08 µg/mL at Weeks 8, 12, and 16, respectively, for the 90 mg single dose group).

In subjects randomized to the placebo group at Week 0 and crossed over to receive 90 mg CNTO 1275 at Week 20, the median serum concentrations of CNTO 1275 were observed to be 1.3, 0.4, and 0.2 µg/mL at Weeks 28, 32, and 36, respectively. They were similar to the serum levels observed at Weeks 8, 12, and 16 (1.1, 0.6, and 0.2 µg/mL, respectively) in subjects originally randomized to receive 90 mg CNTO 1275 at Week 0.

Pharmacokinetic Parameters:

Data Exclusion:

Data from 18 subjects in the active treatment groups (4 subjects in the 45 mg single dose group, 4 subjects in the 90 mg single dose group, 4 subjects in the 45 mg weekly × 4 group, and 6 subjects in the 90 mg weekly × 4 group) were excluded from analyses of

derived PK parameters because of: 1) insufficient blood sampling; 2) incomplete dosing; or 3) poorly characterized terminal elimination phase (defined as $R^2 < 0.90$). Note, however, that the C_{max} and t_{max} values from subjects with poorly characterized terminal elimination phase were included in the summary statistics.

The 18 subjects excluded from PK parameter analysis are as follows. Subject 021-002 (90 mg single dose) had serum CNTO 1275 concentrations available at only 3 timepoints before Week 16 (Days 1, 4 and 8). As a result, the PK parameters could not be estimated from this subject. Subject 020-004 (45 mg weekly \times 4) and Subjects 001-017 and 002-011 (90 mg weekly \times 4) were treated with only 1 dose of CNTO 1275, and Subject 003-006 (90 mg weekly \times 4) was treated with only 2 doses of CNTO 1275. Consequently, these 4 subjects were excluded from the PK analysis. In addition, Subjects 015-018, 020-008, 026-003, and 030-004 (45 mg single dose); Subjects 001-014, 004-020, and 005-008 (90 mg single dose); Subjects 001-016, 021-003, and 021-012 (45 mg weekly \times 4); and Subjects 005-007, 021-013, and 030-001 (90 mg weekly \times 4) exhibited poorly characterized terminal elimination phases after the single or the fourth dose, and the λ_z values could not be reliably estimated. Therefore, the $t_{1/2}$ values from these subjects and associated AUC, AUC (0-t), CL/F, Vz/F, and MRT values were excluded from the summary statistics. Moreover, Subjects 005-006 and 021-004 exhibited poorly characterized terminal elimination phases after the retreatment dose at Week 16. Consequently, the terminal $t_{1/2}$ values for the retreatment dose ($t_{1/2_r}$) calculated from both subjects were also excluded from the summary statistics

Absorption, Distribution and Elimination

CNTO 1275 was slowly absorbed into the systemic circulation with a median t_{max} occurring between 7.0 days (90 mg) and 13.5 days (45 mg) after a single SC administration. It was slowly eliminated from the circulation with a median $t_{1/2}$ estimated from 19.8 days (45 mg) to 21.2 days (90 mg). Overall, the C_{max} and AUC of CNTO 1275 appeared to increase proportionally with the dose at 45 and 90 mg dose levels. A 2-fold increase in dose from 45 mg to 90 mg resulted in an approximate 2.2-fold (5.3/2.4) increase in the median C_{max} and an approximate 2.7-fold (226.9/84.9) increase in the median AUC, demonstrating dose-dependent drug exposure of CNTO 1275. Meanwhile, the CL/F, $t_{1/2}$, and MRT values appeared to be dose independent at these dose levels. The median CL/F values were 5.3 and 4.5 mL/day/kg at the doses of 45 and 90 mg, respectively.

Table 3 Summary of derived pharmacokinetic parameters of ustekinumab

CNTO 1275

	Placebo → 90 mg (at week 20)	45 mg (single dose)	90 mg (single dose)	45 mg (weekly x 4)	90 mg (weekly x 4)
Subjects treated	49	63	64	63	62
Subjects in PK subgroup	16	23	37	23	21
C_{max} (µg/mL)*					
n	0	22	24	23	20
Mean ± SD	NA ± NA	2.7 ± 1.3	6.1 ± 3.6	13.6 ± 5.7	22.9 ± 13.1
Median	NA	2.4	5.3	13.5	20.3
IQ range	(NA, NA)	(1.7, 3.5)	(2.9, 8.0)	(8.7, 17.6)	(14.4, 27.5)
Range	(NA, NA)	(1.0, 5.4)	(1.2, 12.3)	(2.9, 24.1)	(8.0, 63.9)
t_{max} (day)*					
n	0	22	24	23	20
Mean ± SD	NA ± NA	15.3 ± 11.5	9.9 ± 7.4	5.7 ± 7.6	6.7 ± 5.2
Median	NA	13.5	7.0	3.0	3.0
IQ range	(NA, NA)	(6.9, 23.9)	(3.4, 15.3)	(2.0, 3.9)	(2.9, 13.0)
Range	(NA, NA)	(1.9, 38.2)	(2.9, 27.1)	(0.9, 35.0)	(0.9, 14.0)
AUC (0-4) (µg · day/mL)*					
n	0	18	21	0	0
Mean ± SD	NA ± NA	113.4 ± 83.3	241.7 ± 154.7	NA ± NA	NA ± NA
Median	NA	82.6	221.3	NA	NA
IQ range	(NA, NA)	(50.5, 175.0)	(110.6, 302.5)	(NA, NA)	(NA, NA)
Range	(NA, NA)	(31.2, 317.1)	(55.5, 654.9)	(NA, NA)	(NA, NA)

CNTO 1275

	Placebo → 90 mg (at week 20)	45 mg (single dose)	90 mg (single dose)	45 mg (weekly x 4)	90 mg (weekly x 4)
AUC (µg · day/mL)					
n	0	18	21	0	0
Mean ± SD	NA ± NA	196.7 ± 298.2	274.9 ± 206.5	NA ± NA	NA ± NA
Median	NA	84.9	226.9	NA	NA
IQ range	(NA, NA)	(51.0, 186.6)	(113.0, 321.1)	(NA, NA)	(NA, NA)
Range	(NA, NA)	(31.2, 1261.9)	(57.1, 755.5)	(NA, NA)	(NA, NA)
t_{1/2} (day)					
n	10	18	21	20	17
Mean ± SD	30.9 ± 27.5	45.6 ± 80.2	26.7 ± 19.3	24.9 ± 7.9	28.1 ± 7.3
Median	22.3	19.8	21.2	21.3	29.5
IQ range	(19.3, 27.2)	(13.4, 39.3)	(19.1, 24.4)	(19.3, 31.3)	(24.4, 32.1)
Range	(15.7, 107.4)	(5.0, 353.6)	(13.6, 85.8)	(14.5, 46.0)	(12.6, 40.7)
CL/F (mL/day/kg)					
n	0	18	21	0	0
Mean ± SD	NA ± NA	5.8 ± 3.5	5.7 ± 3.6	NA ± NA	NA ± NA
Median	NA	5.3	4.5	NA	NA
IQ range	(NA, NA)	(3.3, 8.1)	(3.2, 8.0)	(NA, NA)	(NA, NA)
Range	(NA, NA)	(0.2, 12.9)	(1.5, 14.9)	(NA, NA)	(NA, NA)

CNTO 1275					
	Placebo → 90 mg (at week 20)	45 mg (single dose)	90 mg (single dose)	45 mg (weekly x 4)	90 mg (weekly x 4)
VzF (mL/kg)					
n	0	18	21	0	0
Mean ± SD	NA ± NA	160.5 ± 64.5	178.7 ± 85.2	NA ± NA	NA ± NA
Median	NA	154.2	160.5	NA	NA
IQ range	(NA, NA)	(116.3, 191.3)	(120.5, 230.4)	(NA, NA)	(NA, NA)
Range	(NA, NA)	(32.6, 280.5)	(37.3, 354.1)	(NA, NA)	(NA, NA)
MRT (day)					
n	0	18	21	0	0
Mean ± SD	NA ± NA	70.2 ± 116.3	43.7 ± 22.0	NA ± NA	NA ± NA
Median	NA	34.9	39.2	NA	NA
IQ range	(NA, NA)	(26.1, 54.0)	(31.2, 41.4)	(NA, NA)	(NA, NA)
Range	(NA, NA)	(10.7, 517.5)	(25.4, 108.4)	(NA, NA)	(NA, NA)

CNTO 1275 also exhibited slow absorption and slow elimination following multiple SC administrations. The median t_{max} occurred approximately 3.0 days (both 45 and 90 mg Weekly x 4 groups) after the fourth dose at Week 3 and the median $t_{1/2}$ values were calculated as from 21.3 days (45 mg weekly x 4) to 29.5 days (90 mg weekly x 4). ***Because of the limited sampling schedule after the fourth dose, the C_{max} and t_{max} values reported for the multiple dose groups should be interpreted with caution.***

In subjects who were randomized to the placebo group at Week 0 and crossed over to receive 90 mg CNTO 1275 at Week 20, the median $t_{1/2}$ value was estimated to be 22.2 days, similar to the median $t_{1/2}$ value calculated from subjects originally randomized to receive a single dose of 90 mg CNTO 1275 at Week 0 (21.2 days). In the 45 mg single dose, 90 mg single dose, and 45 mg weekly x 4 groups, the median $t_{1/2}$ values following the original single or multiple doses were similar between subjects with PGA scores of < 3 who received placebo at Week 16 (approximately 21 to 24 days) and subjects with PGA ≥ 3 who were retreated with CNTO 1275 at Week 16 (approximately 20 to 25 days). ***The comparison could not be made for the 90 mg weekly x 4 groups because only 1 subject had PGA ≥ 3 and was retreated with CNTO 1275 at Week 16. Because of the limited number of subjects enrolled in the PK substudy and the substantial interindividual variability in the pharmacokinetics of CNTO 1275, other meaningful PK comparisons between subjects with PGA scores < 3 who received placebo at Week 16 and subjects with PGA ≥ 3 who were retreated with CNTO 1275 at Week 16 could not be done with statistical validity.***

For subjects with PGA ≥ 3 who were retreated with CNTO 1275 at Week 16, the median $t_{1/2}$ values calculated after the retreatment dose ranged from approximately 17 to 24 days in the 45 mg single dose, 90 mg single dose, and 45 mg weekly x 4 groups. These values were generally consistent with those values calculated after the original single or weekly x 4 doses (approximately 20 to 25 days). ***Again, because of the limited number of subjects available in each retreatment group, this comparison should be interpreted with caution.***

Antibodies to CNTO 1275:

The presence of antibodies to CNTO 1275 was evaluated on blood drawn from all subjects at baseline, Weeks 16 and 20 (preinjection), and Weeks 24, 32, 36, and 52. Table 8 summarizes the incidence and titer of antibodies to CNTO 1275 through Week 52 for subjects who received CNTO 1275 at Week 20 (placebo → 90 mg) or who received CNTO 1275 beginning at Week 0. Of the 293 subjects in the CNTO 1275 groups with appropriate samples for analysis (i.e., had at least 1 sample evaluated after the first injection or had one or more samples available after their last injection through Week 52), the incidence of antibodies to CNTO 1275 through Week 52 was 4.1% (12/293). Three (5.0%) subjects in the 45 mg single dose group, 2 (3.2%) in the 90 mg single dose group, 3 (4.9%) in the 45 mg weekly × 4 group, and 2 (3.3%) in the 90 mg weekly × 4 group were positive for antibodies to CNTO 1275 at some point through Week 52. Of the 49 subjects included in the placebo → 90 mg group, 2 (4.1%) tested positive for antibodies to CNTO 1275 through Week 52. The maximum titers of antibodies to CNTO 1275 ranged from 1:10 to 1:81920.

Among the remaining subjects, 250 (85.3%) subjects in the CNTO 1275 groups were determined to be negative for antibodies to CNTO 1275 through Week 52, while 31 (10.6%) subjects were determined to be inconclusive for antibodies to CNTO 1275. Of the 12 antibody-positive subjects, 4 tested positive for antibodies to CNTO 1275 at Week 16. Antibody titers increased in 2 subjects: from 1:5120 to 1:81920 in Subject 003-007 (45 mg single dose) between Weeks 16 and 20 and from 1:40 to 1:80 in Subject 040-003 (45 mg weekly × 4) between Weeks 16 and 24. Both subjects were retreated with CNTO 1275 at Week 16. Subject 003-007 continued to test positive through Week 52, although antibody titer dropped to 1:640. Subject 040-003 tested negative for antibody to CNTO 1275 by Week 52.

At Week 52, 8 of the 12 antibody-positive subjects had samples evaluated for antibodies to CNTO 1275. Seven of the 8 subjects tested antibody-negative at the Week 52 analysis. All of the patients who tested antibody-negative had previously had low titer (\leq 1:80) antibodies to CNTO 1275 at least 1 visit.

Table 4 Summary of antibody to CNTO 1275 status through week 52; treated subjects

	CNTO 1275					Combined
	Placebo → 90 mg (at week 20)	45 mg (single dose)	90 mg (single dose)	45 mg (weekly x 4)	90 mg (weekly x 4)	
Subjects treated	49	63	64	63	62	301
Subjects with appropriate samples ^a	49	60	62	61	61	293
Subjects positive for antibodies to CNTO 1275 at any time ^{b,c}	2 (4.1%)	3 (5.0%)	2 (3.2%)	3 (4.9%)	2 (3.3%)	12 (4.1%)
Titers						
1:10	2	1	1	1	1	6
1:20	0	1	0	0	1	2
1:40	0	0	0	1	0	1
1:80	0	0	0	1	0	1
1:1280	0	0	1	0	0	1
1:5120	0	0	0	0	0	0
1:81920	0	1	0	0	0	1
Subjects negative for antibodies to CNTO 1275 after last treatment ^{d,e}	41 (83.7%)	53 (88.3%)	55 (88.7%)	53 (86.9%)	48 (78.7%)	250 (85.3%)
Subjects with inconclusive status after last treatment ^e	6 (12.2%)	4 (6.7%)	5 (8.1%)	5 (8.2%)	11 (18.0%)	31 (10.6%)

a Subjects with appropriate samples either had antibodies to CNTO 1275 at some timepoint following their first injection or had 1 or more samples obtained after their last injection.

b Denominator is subjects with appropriate samples.

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

d Includes all subjects who had at least 1 negative sample after their last injection and excludes subjects who were positive.

e Includes subjects whose samples after their last injection were all inconclusive and excludes subjects who were positive.

No impact of antibodies on efficacy was observed, although the small number of subjects with a positive response (12/293) precludes definitive conclusions.

Reviewer's Comments: The dosing regimen used in this study is different from that used in the Phase 3 trials therefore this immunogenicity data may not be applicable to the proposed dosing regimen that was studied in the Phase 3 trials because the immune response may change with changes in dosing frequency.

Pharmacodynamics:

PD assessments included the evaluation of biomarkers associated with the pathogenesis of psoriasis in whole blood and serum, including evaluation of cytokine production in vitro. Punch biopsies from representative target lesions were obtained from 38 subjects at baseline and Week 12 to evaluate the effect of CNTO 1275 on the histopathology of plaque type psoriasis. The applicant stated that the analyses of these biopsies as well as serum biomarkers are ongoing and are to be presented in a separate report.

Cellular Biomarkers: Cell Surface Markers

Peripheral whole blood samples were collected from a subset of 38 subjects at baseline and prior to study agent administration at Week 12. Whole blood staining was performed for selected cell surface markers that are associated with the pathogenesis of psoriasis. The T cell subsets examined include CD3+CD45RA+, CD3+CD45RO+, CD3+CD25+, CD3+HLADR+, CD3+CLA+, and CD3+CXCR3+. There was minimal variation in the major immune cell populations after initiation of various doses of CNTO 1275 compared with placebo. The only notable effect was a decreasing trend with respect to CLA+ T cells after CNTO 1275 treatment.

Cytokine Analysis

Increased Th1, and not Th2, cytokine responses have been associated with active psoriasis. Production of cytokines associated with Th1 and Th2 were analyzed using ELISPOT assays. No spontaneous release (unstimulated condition) of IFN γ , a Th1 cytokine, was observed in either the placebo or the CNTO 1275 groups. Stimulation with a plant lectin (PHA) resulted in unchanged Th1 responses from baseline to Week 12 post-treatment as indicated by the number of IFN γ secreting cells. Th1 reactivity was maintained during treatment, with a trend towards decreasing IFN γ response with the highest dose with PHA stimulation. Stimulation with a bacterial superantigen (SEB) resulted in variable responses in the placebo and CNTO 1275 groups. All groups showed appreciable reactivity to PMA and ionomycin indicating unaltered functional state of the cells.

No spontaneous release (unstimulated condition) of IL-5, a Th2 cytokine, was observed in the placebo and CNTO 1275 groups. Stimulation with PHA demonstrated an increase in Th2 response in the weekly \times 4 groups (highest in 90 mg weekly \times 4 group); however, this increase was not reflected in the single dose groups. Overall, results from IL-5 responses indicate that Th2 responses did not decrease with CNTO 1275 treatment across all dose groups, and the ability to produce IL-5 in the treated groups was similar to that in the placebo group.

Results from Th1/Th2 cytokine analysis showed that the ability to generate both Th1 (IFN γ) and Th2 (IL-5) responses was not affected by CNTO 1275 treatment. ***Serum levels of Th1/Th2 cytokines are being analyzed in a subset of subjects and are to be presented in a separate report.***

Reviewer's Comments: As the applicant stated, the analyses of these biopsies as well as serum biomarkers are ongoing and are to be presented in a separate report, therefore, it is not possible to draw any definitive conclusions regarding the mechanism of action of ustekinumab based on these results at this time

Pharmacokinetic Summary

- CNTO 1275 was slowly absorbed into the systemic circulation (median tmax approximately 7 to 13 days) and was slowly eliminated from the circulation (median t1/2 approximately 20 to 22 days) after a single SC administration.
- Following 4 weekly SC administrations (45 or 90 mg), CNTO 1275 was slowly eliminated from the circulation (median t1/2 approximately 21 to 29 days).
- The extent of CNTO 1275 exposure (Cmax and AUC) appeared to increase proportionally with dose after a single 45 or 90 mg SC administration. The CL/F, t1/2 and MRT appeared to be dose-independent at these levels.

CNTO 1275 Antibody Data Summary

The overall incidence of subjects positive for antibodies to CNTO 1275 through Week 52 was 4.1% (12 subjects).

Pharmacodynamic Summary

- Compared with placebo, treatment with CNTO 1275 overall did not result in notable modulation in percentages of CD3+ T cell subsets in any of the CNTO 1275 dose groups.
- Decreasing trends in skin homing molecule, CLA, were observed in CNTO 1275 dose groups compared with placebo.
- It appears that Th1 reactivity was maintained during treatment with CNTO 1275. A trend towards decreasing IFN γ response was noted with the highest dose of mitogen (PHA), reflecting T cell immunoreactivity.

Reviewer's Comments: Since these studies were exploratory, firm conclusions cannot be drawn regarding the mechanism of action of ustekinumab based on these results.

Applicants Discussions

Fixed dose regimens, not weight-based regimens, were examined, and response rates appeared to be affected by subject weight, with higher efficacy observed in low weight (≤ 95 kg) subjects. Interestingly, the impact of weight was greatest in the groups that received a single 45 or 90 mg dose of CNTO 1275, but the disparity in response rates was minimal in groups that received weekly x 4 CNTO 1275 doses. Thus it appears that some level of dose flexibility may be appropriate to achieve optimal efficacy in heavier subjects. However, significant proportions of subjects in both the higher and lower strata responded to all doses and regimens examined. Additional study is warranted to determine the impact of weight on optimal dosage and administration.

Reviewer's Comments: Based on this data the Phase 3 trials were stratified for weight.

PK analysis demonstrated that CNTO 1275 was slowly absorbed into the systemic circulation (median t_{max} approximately 7 to 13 days) and was slowly eliminated from the circulation (median $t_{1/2}$ approximately 21 to 22 days). These PK values are consistent with those obtained from the Phase 1 Study C0379T02. Both time- and dose-dependent improvement in PASI in subjects treated with single or multiple doses of CNTO 1275 suggest that clinical response to CNTO 1275 might be achieved by optimizing the dose and dosing regimens.

With short-term use, the immunogenicity profile of CNTO 1275 appears acceptable. No concomitant immunosuppressive medications were allowed, yet only 4.1% of subjects developed antibodies to CNTO 1275. No dose-response relationship in the proportions of subjects who developed antibodies to CNTO 1275 was observed, and no correlation was observed between antibodies to CNTO 1275 and injection site reactions, which is especially notable since 4 subjects received doses of CNTO 1275 after testing positive for antibodies to CNTO 1275. In general these data support a relatively low immunogenicity profile for CNTO 1275 either administered to CNTO 1275-naïve subjects with psoriasis or following a gap (> 13 weeks) in treatment following loss of response.

Reviewer's Comments: This immune response may not be applicable to the dosing regimen studied in the Phase 3 trials and that proposed for marketing.

Study # C0743T11:

Title of Study: A Study to Evaluate the Pharmacokinetics of a Single Subcutaneous Administration of 90 mg CNTO 1275 as Liquid Formulation (1 mL) to Healthy Male Subjects

Investigator(s) and Study Center(s): _____

b(4)

Study Dates: From: March 21, 2006 to: July 3, 2006

Phase of Development: 1

Objectives:

- To evaluate the pharmacokinetic (PK) profile and PK variability of CNTO 1275 following a single subcutaneous (SC) injection of 1 mL of 90 mg/mL CNTO 1275 as a liquid formulation administered to healthy subjects.
- To monitor the safety and tolerability of a single SC injection of the liquid formulation of CNTO 1275 in healthy subjects.

Methodology: This was an open label, single dose study in healthy adult male subjects.

Number of Subjects: Study subjects were healthy male volunteers, 18 to 45 years old, with a body mass index (BMI) of 23-30 kg/m², inclusive, and a weight of 60-90 kg, inclusive. Approximately 30 subjects were enrolled to receive CNTO 1275 such that approximately 24 subjects complete the study. Subjects withdrawn from the study may be replaced at the discretion of the Sponsor.

Reviewer's Comments: The applicant stated that based on the PK data collected up to date, no evidence showed that there is a gender difference in PK. In order to maintain uniformity with future BE studies, the current study population is therefore limited to male subjects. Any potential gender difference in PK will be explored in phase III trials. Since the results of the POPPK analysis did not identify gender as a significant covariate, this seems reasonable.

Test Product, Dose, Mode of Administration:

Each subject received a single 1 mL SC injection of 90 mg CNTO 1275. Subjects fasted from all food and beverages (except water) at least 8 hours prior to drug administration. Subjects may discontinue fasting 4 hours after study agent administration. CNTO 1275 for SC injection was supplied in 2 mL single-use glass vials (consisting of 90 mg/mL) as a sterile liquid, Lot number: D05PE7428

Study Duration: The total duration of subject participation in the study was 114 days.

Screening: Within 30 days prior to dosing

Inpatient Stay: Day -1 (day before dosing), Day 1 (day of dosing), Day 2 to Day 15.

Blood samples were collected for serum concentrations of CNTO 1275 through Day 15 post-dose.

Outpatient Period: Subjects were to visit the study unit on Day 18 and at Weeks 3, 4, 5, 6, 7, 8, 9, 10, and 12 for the blood collection to measure the serum concentration of CNTO 1275 and safety monitoring.

End of Study/ Early Termination Visit: Subjects returned to the clinic in Week 12 for the End of Study procedures including blood collection for measuring serum concentrations of CNTO 1275 and the monitoring of safety parameters.

Pharmacokinetic Sampling:

CNTO 1275 concentrations were determined in serum samples collected at the following times: 1 hour prior to dosing, 12 hours, 24 hr (Day 1), 48 hr (Day 2), 72 hr (Day 3), 96 hr (Day 4), 120 hr (Day 5), 144 hr (Day 6), 168 hr (Day 7), 192 hr (Day 8), 216 hr (Day 9), 240 hr (Day 10), 264 hr (Day 11), 288 hr (Day 12), 312 hr (Day 13), 336 hr (Day 14).

Blood collections for serum concentrations of CNTO 1275 were also performed on Days 17, 21, 28, 35, 42, 49, 56, 63, 70, and 84 post-dosing.

Twenty-six blood samples per subject were collected for serum concentration analysis. A total of 9.5 mL of blood will be collected at each time point. As a result, all subjects had approximately 247 mLs of blood collected for serum concentration and immune response analyses.

Immunogenicity:

Blood samples were collected on Day 1 and Day 84 for the determination of antibodies to CNTO 1275 in serum.

Reviewer's Comments: Sampling allowed for adequate wash-out period.

Bioanalytical Methods:

Pharmacokinetics: Electrochemiluminiscent Immunoassay was used to determine serum CNTO 1275 concentrations. The LOQ of the method was 16.88 ng/mL (0.17 mcg/mL).

Immunogenicity: Analyses for the detection of antibodies to CNTO 1275 in human serum samples were performed using an enzyme immunoassay (EIA). Since CNTO 1275 can interfere with the detection or interpretation of an anti-CNTO 1275 antibody response, all samples evaluated for antibodies to CNTO 1275 were analyzed for CNTO 1275 concentrations. Subjects were defined as follows:

- Subjects were characterized as positive for antibodies to CNTO 1275 if any sample was positive for anti-CNTO 1275 antibodies, regardless of the presence or absence of CNTO 1275 in the samples.
- Subjects were characterized as negative for antibodies to CNTO 1275 if the last serum sample did not contain measurable CNTO 1275 and if antibodies to CNTO 1275 were not detected in all samples evaluated after CNTO 1275 administration.
- Subjects were characterized as undetectable or inconclusive for antibodies if antibodies to CNTO 1275 were not detected in all samples and there were measurable concentrations of CNTO 1275 present in the last serum sample(s) evaluated after CNTO 1275 administration.

Assessments and Statistical Methods:

Pharmacokinetics:

The PK analysis was based on all subjects who had an evaluable concentration-time profile for CNTO 1275. PK parameters were calculated by non-compartmental techniques using WinNonlin 4.1 (Pharsight Corporation, Mountain View, CA). All calculations were based on actual sampling times. Pharmacokinetic parameters included: C_{max}, t_{max}, t_{1/2}, AUC_{last}, AUC_{inf}, AUC (0-63Days), AUC (0-84Days), CL/F, V_z/F:

Descriptive statistics: (N, mean, standard deviation (SD), coefficient of variation (CV%), median, minimum, and maximum, interquartile (IQ) range) were used to summarize PK parameters and serum concentrations at each planned sampling time point.

Efficacy and safety, PK and antibody to CNTO 1275 status by weight (≤ 100 kg, > 100 kg) were assessed.

Immunogenicity:

Frequencies and percentages of subjects with serum samples that were positive, negative, or inconclusive (undetectable) for antibodies to CNTO 1275 are summarized by CNTO 1275 treatment group and the individual serum sample analysis results are listed.

Results:

Disposition of Subjects: Of the 85 subjects screened, 31 subjects were enrolled in the study. The study drug was administered at two different time points, to 21 subjects in the first instance and 10 subjects at the second. All 31 subjects were included in the PK and safety populations. A total of 26 subjects completed the End of Study visit on Day 85. Five subjects withdrew from the study. Two subjects (# 00050 and 00056) withdrew consent each prior to Day 18 and Day 15, respectively. Two subjects were discharged from the study for using unacceptable concomitant medications (alcohol for subject # 00071 and cannabinoids for subject # 00083 both at Week 10), while one subject (# 00001) was a non-completer due to non-compliance with protocol procedures.

Five subjects (00016, 00041, 00045, 00066, and 00072) who did not meet either the weight or BMI criteria for study eligibility were granted waivers to participate in the study by Centocor.

The PK population and safety population included all 31 subjects, including the subject that tested positive for CNTO-1275 antibody (Subject 00006), because all 31 enrolled subjects received the study agent and satisfied all criteria to be included in the PK analysis. However, the PK parameters of Subject 00056 were later excluded from the summaries because of insufficient samples in his profile to compute meaningful PK parameters.

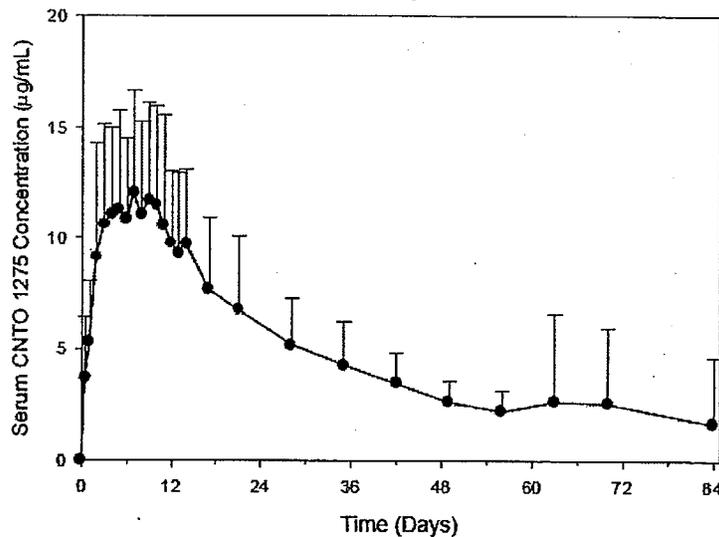
Table 5: Subject Demographics and Baseline Characteristics

Category		90 mg CNTO 1275 N=31
Age (years)	Mean (SD)	24.6 (4.82)
	Median	24.0
	(min, max)	19.0, 43.0
Race n (%)	Caucasian	24 (77.4)
	Black	4 (12.9)
	Asian	0 (0.0)
	Other	3 (9.7)
Weight (kg)	Mean (SD)	80.27 (7.640)
	Median	81.30
	(min, max)	61.3, 94.9
Height (cm)	Mean (SD)	174.68 (6.130)
	Median	175.30
	(min, max)	162.6, 185.4
BMI (kg/m ²)	Mean (SD)	26.31 (2.262)
	Median	26.40
	(min, max)	22.5, 30.3

Pharmacokinetics:

Serum-Concentration-Time Profile:

Figure 9: Mean (SD) Ustekinumab Serum Concentrations over Time after a Single 90 mg SC Dose of Ustekinumab to Healthy Male Volunteers



Subject 00041 exhibited quantifiably low concentration (0.1 µg/mL) of serum CNTO 1275 prior to administration of the study agent. This finding may be a result of matrix interference in the serum concentration assay. CNTO 1275 levels were detected in serum

at the first sampling point (12 hours) post dose and were generally measurable through 84 days following SC injection for most subjects. In general, CNTO 1275 peaked in serum between 4 and 17 days after the dose, subsequently clearing from serum in an apparent mono-exponential manner. Subject 00016 had unusually higher concentrations in the terminal phase and achieved the peak CNTO 1275 levels at 63 days post-dose. This anomaly contributed towards slightly higher mean concentrations in the terminal phase as displayed in the concentration vs. time profile.

Pharmacokinetic Parameters:

Key pharmacokinetic parameters are shown in the table below.

Table 6 A Derived PK Parameters

Parameter	Summary Statistics		
	N	Mean ± SD	CV%
C _{max} (µg/mL)	30	15.17 ± 5.01	33.04
AUC(0-63D) (day*µg/mL)	28	346.24 ± 96.34	27.83
AUC(0-84D) (day*µg/mL)	23	358.81 ± 106.70	29.74
AUC _{last} (day*µg/mL)	30	386.02 ± 138.19	35.80
AUC _{inf} (day*µg/mL)	23	399.81 ± 135.65	33.93
V _z /F (L)	23	7.36 ± 2.95	40.06
CL/F (L/day)	23	0.25 ± 0.10	40.29
		Median (Range)	
t _{max} (day)	30	8.50 (7.00-11.00)	101.74
t _{1/2} (day)	23	20.35 (15.63-24.78)	54.82

The following findings are based upon the pharmacokinetic results:

- CNTO 1275 in serum was generally measurable through 84 days following a SC administration of 90 mg CNTO 1275 for most subjects.
- CNTO 1275 levels in serum achieved the maximum concentration at a median time of 8.5 days.
- CNTO 1275 was slowly eliminated from serum with a median terminal half-life of 20.35 days and an apparent clearance of about 0.25 L/day.
- C_{max}, AUC (0-63D), AUC(0-84D), and AUC_{inf} showed CV of 33.04%, 27.83%, 29.74%, and 33.93%, respectively, indicative of moderate data variability.

Table 6B : Descriptive Statistics on CNTO 1275 Serum Pharmacokinetic Parameters Following a Single SC 90 mg Dose of CNTO 1275 to Healthy Male Subject

Parameter	Statistic						
	N	Mean	SD	CV%	Median	IQ Range	Range
C _{max} (µg/mL)	30	15.17	5.01	33.04	15.31	10.57-19.34	7.69-23.84
AUC(0-63D) (day*µg/mL)	28	346.24	96.34	27.83	324.39	288.02-432.99	144.09-591.27
AUC(0-34D) (day*µg/mL)	23	358.81	106.70	29.74	344.77	281.43-404.26	146.57-649.06
AUC _{last} (day*µg/mL)	30	386.02	138.19	35.80	369.58	307.35-474.32	128.69-799.78
AUC _{inf} (day*µg/mL)	23	399.81	135.65	33.93	365.95	314.37-490.28	147.40-731.32
t _{max} (day)	30	10.23	10.41	101.74	8.50	7.00-11.00	4.00-63.00
t _{1/2} (day)	23	22.07	12.10	54.82	20.35	15.63-24.78	4.23-69.38
V _z /F (L)	23	7.36	2.95	40.06	7.28	5.15-9.12	2.56-13.54
V _z /F (mL/kg)*	23	90.21	33.08	36.67	85.77	64.29-112.81	29.04-156.12
CL/F (L/day)	23	0.25	0.10	40.29	0.25	0.18-0.29	0.12-0.61
CL/F (mL/day/kg)*	23	3.11	1.11	35.78	3.03	2.40-3.32	1.53-7.04

Changes in the Conduct of the Study or Planned Analyses:

An additional PK parameter, AUC (0-63D), was estimated after it was determined that CNTO 1275 in serum was detectable until that time point in most subjects. Additionally, individual subject body weight adjusted V_z/F and CL/F were derived and summarized after the database lock. These parameters were not defined in the SAP. Overall 16 subjects were administered a dose of CNTO 1275 which exceeded the protocol allowable limit of 5% deviation from 90 mg/mL per injection. The maximum deviation was 7.5%. All the subjects were included in the PK population.

Immunogenicity:

Of the 29 subjects who had appropriate samples to test for antibodies to CNTO 1275, 1 subject (3.4%) was classified as positive for antibodies to CNTO 1275 through Week 12. This subject's V_z/F (2.56 L) and t_{1/2} (4.23 days) values were at the lowest end of ranges observed for the PK population in this study. Two subjects (6.9%) were classified as negative for antibodies to CNTO 1275 and 26 subjects (89.7%) were classified as undetectable (or inconclusive) for antibodies.

Conclusions:

Based on the PK results, the following pharmacokinetic conclusions can be drawn:

- CNTO 1275 in serum was generally measurable through 84 days following an SC administration of 90 mg CNTO 1275 for most subjects.
- CNTO 1275 levels in serum achieved the maximum concentration at a median time of 8.5 days.
- CNTO 1275 was slowly eliminated from serum with a median terminal half-life of 20.35 days and an apparent clearance of about 0.25 L/day.
- C_{max}, AUC(0-63D), AUC(0-84D), and AUC_{inf} showed CV of 33.04%, 27.83%, 29.74%, and 33.93%, respectively, indicative of moderate PK variability of CNTO 1275.
- The apparent volume of distribution was approximately 7 liters, similar to that of the blood volume.
- As an exception, CV% on t_{max} was 101.7%, which was possibly contributed by an anomalous delay in t_{max} for Subject 00016.

Reviewer's Comments: Applicant's conclusions are reasonable.

Study Reports of Controlled Clinical Studies

Study # C0743T08

Reviewer's Comments: Please note that this reviewer will only be focusing on the PK and the effect of immunogenicity on PK component of this study report. The clinical reviewer (Dr. B. Carr will be reviewing the efficacy and safety component).

Title of the study: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Evaluating the Efficacy and Safety of CNTO 1275 in the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis

Study Name: Phoenix 1

Principal/Coordinating Investigator(s): Craig Leonardi, MD, Central Dermatology, PC, 1034 S. Brentwood Blvd., Suite 600, St. Louis, MO 63117

Study Center(s): 48 investigative sites: 29 sites in the US, 16 sites in Canada, and 3 sites in Belgium

Studied Period: 15 Dec 2005/12 Apr 2007

Phase of Development: 3

Objectives: The primary objective of this study was to evaluate the efficacy and safety of CNTO 1275 in the treatment of subjects with moderate to severe plaque psoriasis.

The secondary objectives were to: (1) Evaluate the maintenance of response with CNTO 1275 and (2) Evaluate the impact of CNTO 1275 on quality of life (QOL).

Methodology: This is a multi-center, randomized, placebo-controlled, double-blind, parallel, 3-arm study of SC injections of 45 mg (Group 1), 90 mg (Group 2), and placebo (Group 3) in subjects with moderate to severe plaque psoriasis.

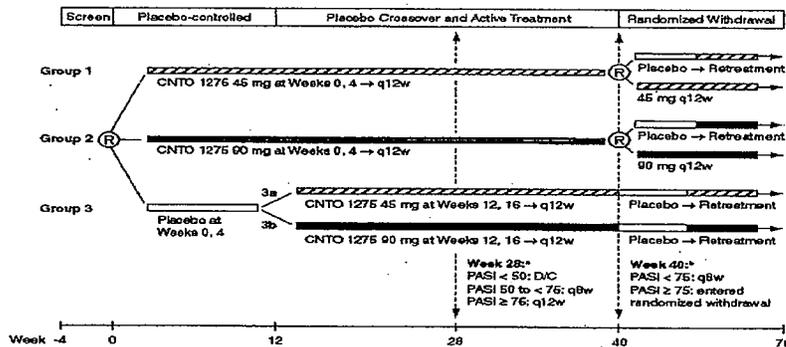
The study consists of 4 study periods occurring over approximately 5 years:

- A 12-week placebo-controlled period
- A subsequent 28-week placebo crossover and active treatment period
- A randomized-withdrawal period after Week 40;
- A long term extension period begins at Week 52 for an additional 4 years

Number of Subjects (Planned and Analyzed): 750 planned (250 subjects per group)

Diagnosis and Main Criteria for Inclusion: Men or women ages 18 years or older with moderate to severe plaque psoriasis who have a Psoriasis Area and Severity Index (PASI) ≥ 12 , and at least 10% of their total body surface area (BSA) involved and were considered by the investigator to be candidates for phototherapy or systemic therapy. Appropriate washout periods were specified for prior use of other biologics, investigational drugs, immunosuppressants, vaccines, and systemic or topical treatments that could affect psoriasis or PASI evaluations.

Test Product, Dose and Mode of Administration, Batch Number 45 or 90 mg CNTO 1275 (0.5 or 1.0 mL, respectively) was administered by SC injection. Subjects randomized to the 45 or 90 mg CNTO 1275 groups were to receive CNTO 1275 at Weeks 0, 4, and 16. At Week 12, subjects randomized to placebo at Week 0, were to receive 45 mg or 90 mg CNTO 1275 at Weeks 12 and 16. Subsequent dosing regimens were to be determined by each subject's response status according to the study design. Two lots of CNTO 1275 (D05PE7427 and D05PE7428) were used in the study.



D/C = discontinued; PASI = Psoriasis Area and Severity Index; @ = randomization; q8w = every 8 weeks; q12w = every 12 weeks
^a At Week 28, in all groups, nonresponders (PASI < 50) discontinued study agent, partial responders (PASI 50 to < 75) began q8w dosing, and PASI responders (PASI ≥ 75) received q12w dosing.
^b At Week 40, PASI responders to q12w dosing in Groups 1 and 2 were randomized to either placebo or continued q12w CNTO 1275 (at their original dose), while those in Group 3 received placebo. At loss of therapeutic effect, subjects receiving placebo began retreatment at their dosing regimen prior to withdrawal. In all groups, nonresponders or partial responders (PASI < 75) were adjusted to q8wk dosing. Subjects receiving q8w dosing continued q8w dosing.

Figure 10: Study Design Overview

Study agent was to be initially administered at the investigator site by an appropriately licensed and authorized health professional for the first 12 weeks (i.e., up to 2 doses). After Week 12 and at the discretion of the investigator and subject, and after appropriate training, study agent could be self-administered at the investigative site by the subject. All subjects were strongly encouraged to self-inject by Week 40. Specific instructions for injection of study agent were supplied in the Study Reference Manual. The randomization was stratified by investigational site and baseline weight (≤ 90 kg or > 90 kg).

Duration of Treatment: The first to the last study agent administration was 48 weeks or more; efficacy and safety data were evaluated through the date the last subject completed the Week 52 visit; pharmacokinetic and antibodies to CNTO 1275 data were evaluated through Week 52.

Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo was administered by SC injection. Subjects randomized to placebo were to receive 2 placebo injections (0.5 mL and 1.0 mL) at Weeks 0 and 4. Subjects randomized to the CNTO 1275 groups were to receive 2 placebo injections (0.5 mL and 1.0 mL) at Week 12. To maintain the blind associated with CNTO 1275 dose administration, each subject randomized to CNTO 1275 was also given a placebo injection; subjects in the 45 mg group received a 1.0 mL placebo injection, and subjects receiving 90 mg also received a 0.5 mL placebo injection. Two lots of placebo (D05PE7429 and D05PE7430) were used.

Pharmacokinetics: Blood samples for the determination of serum CNTO 1275 concentration were collected at Weeks 0, 4, 12, 16, 24, 28, 40, 44, 48 and 52. At visits when study agent was scheduled, samples were collected just before the study agent was administered.

Immunogenicity: Serum samples were collected from all subjects at baseline, Weeks 12, 40, and 52 to determine the incidence of antibodies to CNTO 1275. At visits when study agent was scheduled, samples were collected just before the study agent was administered.

Reviewer's Comments: These sampling times did not allow for adequate wash-out period of ustekinnab after the last injection was administered.

Bioanalytical Methods: Electrochemiluminiscent Immunoassay was used to determine serum CNTO 1275 concentrations. The LOQ of the method was 16.88 ng/mL (0.17 mcg/mL).

Immunogenicity: Analyses for the detection of antibodies to CNTO 1275 in human serum samples were performed using an enzyme immunoassay (EIA) (see CMC review for details). Since CNTO 1275 can interfere with the detection or interpretation of an anti-

CNTO 1275 antibody response, all samples evaluated for antibodies to CNTO 1275 were analyzed for CNTO 1275 concentrations. Results from analysis of antibodies to CNTO 1275 were classified as positive, negative, or undetectable.

- **Positive:** Samples with detectable antibodies to CNTO 1275 were classified as antibody positive, regardless of the presence or absence of detectable CNTO 1275 concentration in these samples. Subjects with at least 1 positive sample at any timepoint evaluated were classified as antibody positive for their anti-CNTO 1275 immune response status. In the instance that a subject had a positive baseline sample, post administration samples were considered treatment-emergent positives only when their titer was two-fold or higher than the baseline titer.
- **Negative:** Samples without detectable CNTO 1275 concentration and with no detectable antibodies to CNTO 1275 were classified as negative for antibodies to CNTO 1275. Subjects were designated negative for antibodies to CNTO 1275 when there was no positive sample at any time up to the study end point and the last sample was negative.
- **Undetectable:** Samples without detectable antibodies to CNTO 1275 but containing detectable CNTO 1275 concentration were classified as undetectable or inconclusive for antibodies to CNTO 1275. Subjects were designated undetectable for antibodies to CNTO 1275 when there was no positive sample at any time up to the study end point and the last sample was undetectable

Efficacy: The primary endpoint was the proportion of subjects who achieved PASI 75 response at Week 12. Efficacy assessments included PASI and Physician's Global Assessment (PGA). In addition, the relationship between serum CNTO 1275 concentration and efficacy was examined, as well as between antibodies to CNTO 1275 and efficacy.

Safety: Safety was assessed by 1) measurement of vital signs; 2) AEs and SAEs that may have occurred at and between each of the evaluation visits; 3) TB evaluation; 4) changes in routine laboratory analyses (hematology and chemistry); 5) evaluation of fasting glucose, hemoglobin A1c, C-reactive protein (CRP), and D-dimer at selected time points.

Statistical Methods: Simple descriptive statistics, such as mean, median, SD, interquartile (IQ) range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables were used to summarize most data.

In addition, serum CNTO 1275 concentration-time data collected from this study was included in a Population PK analysis to estimate the apparent CL/F and the apparent volume of distribution V/F of CNTO 1275. In addition the POPPK analysis was used to identify and quantify factors, such as demographics or baseline physical and biochemical characteristics that may affect the pharmacokinetics of CNTO 1275 in subjects with psoriasis (see Pharmacometrics review for details).

Results:

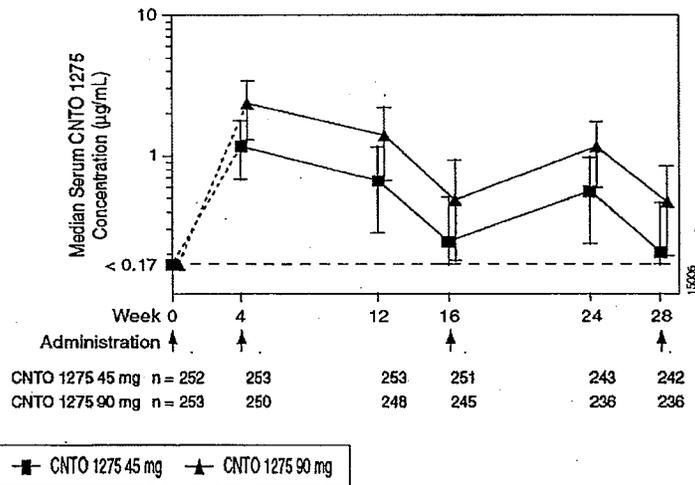
Study Population: A total of 766 subjects were randomized. The majority (69.3%) of subjects were men, most subjects were Caucasian (93.6%), and the median age and body

weight of subjects was 45.5 years (range: 19 to 76 years) and 91.6 kg (range: 46.9 to 183.2 kg), respectively. The median duration of psoriasis was 18.3 years. The population spanned moderate to severe psoriasis, with a median BSA of 21.0% and a median PASI score of 17.6 and 43.7% had a PGA of marked or severe. Seven hundred and fifty one (751) subjects had samples available for the pharmacokinetics analysis; 743 subjects were analyzed for antibodies of CNTO 1275.

Pharmacokinetic Results:

Plasma Concentration-Time Profiles:

Figure 11 Median with IQ range of the serum CNTO 1275 concentrations (micrograms/mL) through Week 28; subjects randomized to CNTO 1275 groups at Week 0



At each sampling time point from week 4 through week 28, median serum CNTO 1275 concentrations were higher in the 90 mg group than the 45 mg group with differences between the 2 groups showing approximate dose proportionality. The median trough serum concentrations of CNTO 1275 at Week 4, 16 and 28 were 1.17, 0.25 and 0.21 mcg/mL (45 mg group) and 2.38, 0.49 and 0.47 mcg/mL (90 mg group), respectively.

Table 7: Summary of CNTO 1275 concentrations (micrograms/mL) through Week 28; treated subjects with CNTO 1275

CNTO 1275				
	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg
Subjects treated with CNTO 1275	123	120	255	255
Week 0				
n	121	118	252	253
Mean ± SD	0.00 ± 0.035	0.00 ± 0.019	0.00 ± 0.000	0.00 ± 0.027
Median	0.00	0.00	0.00	0.00
IQ range	(0.00, 0.00)	(0.00, 0.00)	(0.00, 0.00)	(0.00, 0.00)
Range	(0.0, 0.3)	(0.0, 0.2)	(0.0, 0.0)	(0.0, 0.5)
Week 4				
n	123	118	253	250
Mean ± SD	0.00 ± 0.035	0.00 ± 0.029	1.50 ± 5.426	2.52 ± 1.527
Median	0.00	0.00	1.17	2.38
IQ range	(0.00, 0.00)	(0.00, 0.00)	(0.68, 1.78)	(1.30, 3.42)
Range	(0.0, 0.3)	(0.0, 0.3)	(0.0, 54.1)	(0.0, 9.2)
Week 12				
n	123	119	253	248
Mean ± SD	0.01 ± 0.044	0.00 ± 0.000	0.89 ± 1.594	1.59 ± 1.208
Median	0.00	0.00	0.67	1.41
IQ range	(0.00, 0.00)	(0.00, 0.00)	(0.29, 1.17)	(0.68, 2.23)
Range	(0.0, 0.4)	(0.0, 0.0)	(0.0, 23.4)	(0.0, 6.1)
Week 16				
n	122	118	251	245
Mean ± SD	1.27 ± 0.835	2.56 ± 1.586	0.37 ± 0.717	0.66 ± 0.686
Median	1.17	2.26	0.25	0.49
IQ range	(0.71, 1.74)	(1.45, 3.20)	(0.00, 0.51)	(0.18, 0.94)
Range	(0.0, 4.1)	(0.0, 9.0)	(0.0, 9.4)	(0.0, 4.1)
Week 24				
n	123	119	243	236
Mean ± SD	0.79 ± 0.700	1.52 ± 1.351	0.85 ± 1.872	1.40 ± 1.578
Median	0.68	1.13	0.56	1.17
IQ range	(0.28, 1.12)	(0.58, 2.27)	(0.24, 0.98)	(0.60, 1.75)
Range	(0.0, 3.9)	(0.0, 7.7)	(0.0, 26.1)	(0.0, 19.8)
Week 28				
n	122	116	242	236
Mean ± SD	0.33 ± 0.387	0.70 ± 0.808	0.33 ± 0.736	0.59 ± 0.601
Median	0.28	0.49	0.21	0.47
IQ range	(0.00, 0.51)	(0.21, 0.95)	(0.00, 0.47)	(0.19, 0.85)
Range	(0.0, 2.4)	(0.0, 4.8)	(0.0, 10.0)	(0.0, 3.1)

In the placebo-45 mg and placebo-90 mg groups, the median serum concentrations of CNTO 1275 observed at Weeks 16, 24, and 28 were comparable to those serum concentrations observed at Weeks 4, 12, and 16 in subjects in the 45 mg and 90 mg groups.

Steady State Attainment:

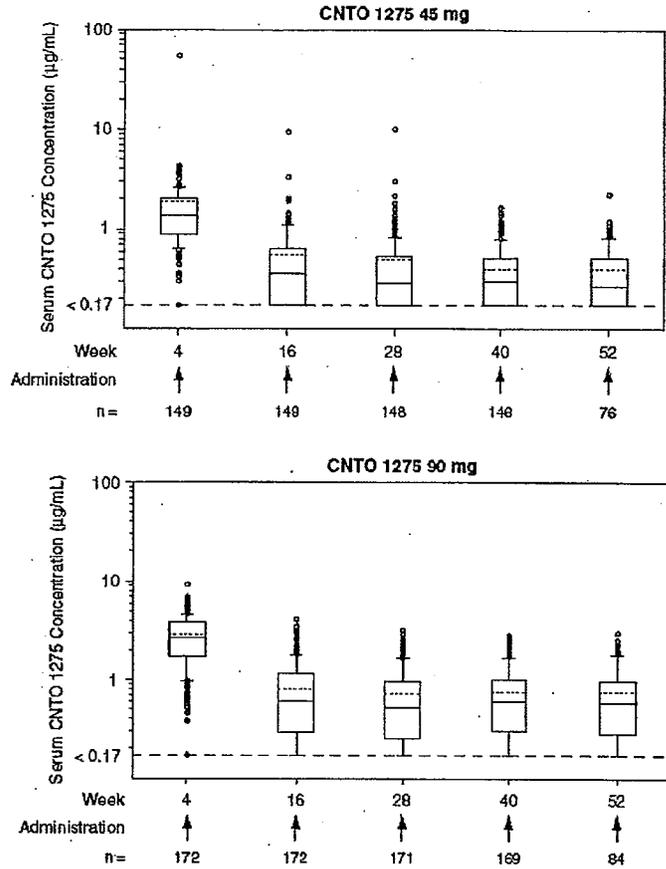


Figure 11 Box plot of pre-injection serum CNTO 1275 concentration (micrograms/mL) through Week 52; treated subjects who were randomized at Week 40

Concentrations at Week 52 represent data from subjects who continued q12w dosing after Week 40. The top and bottom of each box indicate the 25th and 75th percentiles, respectively. The solid line within the box denotes the median; the mean is denoted by a dotted line. The central vertical lines (whiskers) extend from the edge of the box to the 10th and 90th percentiles. Any value exceeding these percentiles is represented with an open circle.

Median trough serum concentrations of CNTO 1275 remained consistent at Weeks 28, 40, and 52, demonstrating that steady state was achieved by Week 28. There was no evidence of accumulation in CNTO 1275 concentrations over time when given subcutaneously q12w.

Impact of Weight on Serum Concentrations:

Because dose-Response in efficacy was most apparent in subjects > 100 kg (see table below), the impact of weight on serum concentrations was examined by classifying subjects' baseline weight into 2 groups: ≤ 100 kg and > 100 kg.

To evaluate the impact of weight on efficacy, PASI 75 response rates at Week 12 were analyzed by approximate weight quartiles and subpopulations based on 10-kg increments in weight (see Table 12). The proportions of PASI 75 responders in subpopulations of subjects in the 45 mg group showed a trend to lower efficacy with increasing weight, both by weight quartiles and by 10-kg increments. In contrast, the proportions of PASI 75 responders in subpopulations of subjects in the 90 mg group showed minimal impact of weight on efficacy by weight quartiles or by 10-kg increments (with the possible exception of subjects > 130 kg). The incremental benefit in efficacy from the 90 mg dosing regimen appeared to emerge in subjects > 100 kg as efficacy differences and in the highest weight quartile (subjects > 105 kg). In subpopulations ≤ 100 kg, a consistent pattern of dose-response was not observed, and response rates were paradoxically higher in the 45 mg group in some 10-kg increment subpopulations (eg, subjects > 80 to ≤ 90 kg). Similar results were observed when psoriasis improvement was measured by PGA.

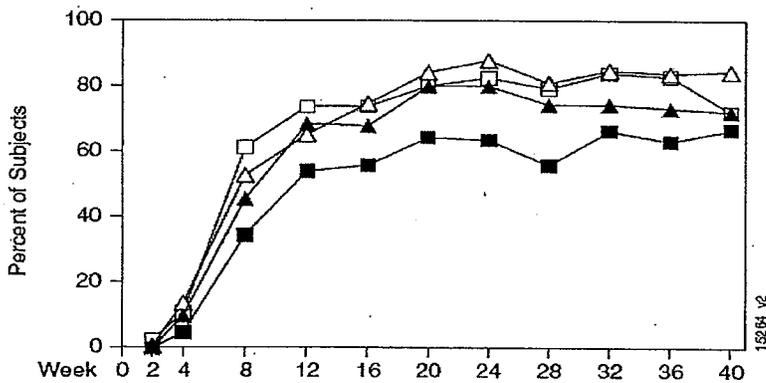
Table 12 Number of PASI 75 responders at Week 12 by body weight (kg) categories; subjects randomized at Week 0

	Placebo	CNTO 1275	
		45 mg	90 mg
Subjects randomized at Week 0	255	255	256
PASI 75 responders at Week 12	8 (3.1%)	171 (67.1%)	170 (66.4%)
Body weight (kg) by quartiles			
≤ 75	5.3% (3/55)	78.1% (50/64)	72.2% (39/54)
> 75 to ≤ 90	4.6% (3/65)	77.2% (44/57)	62.7% (42/67)
> 90 to ≤ 105	1.5% (1/66)	64.5% (40/62)	66.7% (44/66)
> 105	1.4% (1/69)	51.4% (37/72)	65.2% (45/69)
Body weight (kg) by fixed intervals			
≤ 50	0.0% (0/2)	75.0% (3/4)	100.0% (2/2)
> 50 to ≤ 60	15.4% (2/13)	100.0% (10/10)	69.2% (9/13)
> 60 to ≤ 70	4.3% (1/23)	76.9% (20/26)	71.4% (15/21)
> 70 to ≤ 80	3.1% (1/32)	70.5% (31/44)	72.1% (31/43)
> 80 to ≤ 90	4.0% (2/50)	31.1% (30/37)	57.1% (24/42)
> 90 to ≤ 100	0.0% (0/46)	63.8% (30/47)	60.5% (26/43)
> 100 to ≤ 110	3.6% (1/28)	60.0% (18/30)	73.7% (28/38)
> 110 to ≤ 120	0.0% (0/25)	52.6% (10/19)	70.8% (17/24)
> 120 to ≤ 130	7.7% (1/13)	68.8% (11/16)	75.0% (6/8)
> 130	0.0% (0/23)	36.4% (8/22)	54.5% (12/22)

Based on results of efficacy analyses by 10-kg increments, efficacy over time was evaluated in weight subpopulations relative to 100 kg. A dose response relationship was not apparent at any time point through Week 12 for any of these PASI thresholds for subjects ≤ 100 kg. In subjects > 100 kg, differences in PASI 75 response rates between the 45 mg and 90 mg groups were observed by Week 4 and increased through Week 12. A smaller dose response was observed in the high weight stratum when a PASI 50

threshold was used to evaluate efficacy, and no dose response was observed through Week 12 in the high weight stratum as measured by a PASI 90 response. Generally, similar results were observed using a 90 kg threshold, which was the weight threshold used in stratifying the randomization, though the dose-response in the high weight stratum may be modestly lower than that observed when using a 100 kg threshold. Combined, these results suggest that the dose response relationship in efficacy exists primarily in the subpopulation of subjects > 100 kg. Similar dose-response relationships were observed at Week 28 through Week 40.

Figure 12 Percent of subjects achieving PASI 75 response through Week 40 by body weight (≤ 100 kg, > 100 kg); subjects randomized to CNTO 1275 groups at Week 0



CNTO 1275 45 mg

≤ 100 kg	n = 168	168	168	168	168	166	166	164	163	164	162
> 100 kg	n = 87	87	87	87	86	84	85	86	86	84	84

CNTO 1275 90 mg

≤ 100 kg	n = 163	161	159	164	158	158	156	153	151	148	148
> 100 kg	n = 92	92	90	92	90	90	90	90	90	90	90

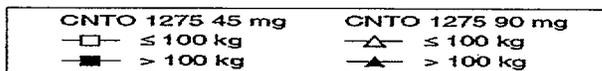
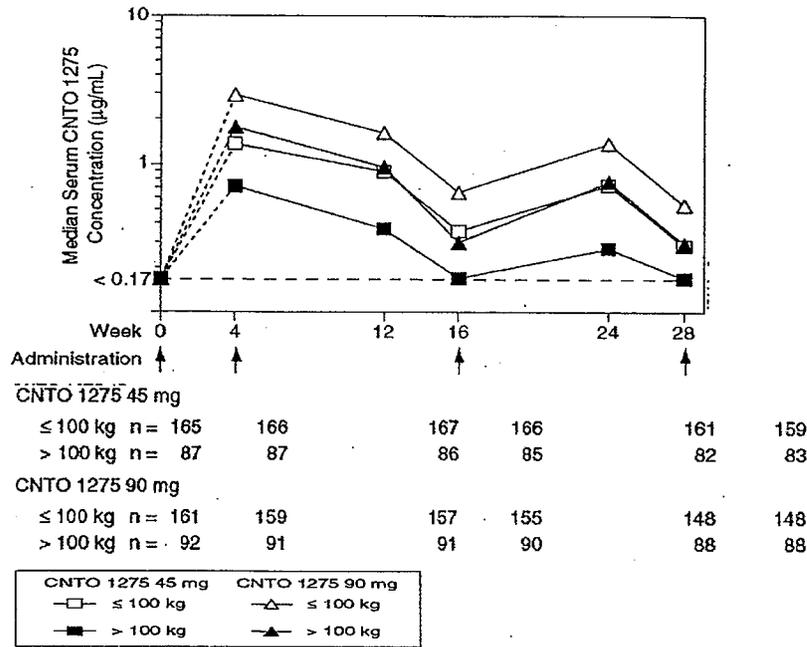


Figure 13 Median serum CNTO 1275 concentrations (micrograms/mL) through Week 28 by body weight (≤ 100 kg, > 100 kg); subjects randomized to CNTO 1275 groups at Week 0



- Subjects of higher weight (> 100 kg) had lower median serum CNTO 1275 concentrations compared with subjects of lower weight (≤ 100 kg).
- Within each dose (i.e. 45 mg and 90 mg), the median trough serum CNTO 1275 concentrations at all the sampling time points in subjects with weights > 100 kg were generally lower (40-60 %) than those at respective time points in subjects with lower weight.
- Across doses, the median trough serum concentrations of CNTO 1275 in subjects of higher weight (> 100 kg) in the 90 mg group were comparable to those in subjects of lower weight (≤ 100 kg) in the 45 mg group at all sampling time points.

Immunogenicity:

The overall incidence of antibodies to CNTO 1275 through Week 52 was 5.1 % (38/743 subjects). The proportion of subjects who were positive for antibodies to CNTO 1275 was higher in the 45 mg group (7.1 %) than the 90 mg group (2.0 %). However, this finding was not observed in the placebo to 45 mg group (5.0%) compared with the placebo to 90 mg group (7.7 %). However, when combined, a trend was observed for a higher proportion of subjects in the combined 45 mg group to be positive for antibodies to CNTO 1275 compared with the combined 90 mg group (24 [6.4%] subjects versus 14 [3.8%] subjects). Lower immunogenicity in 90 mg group may be due to higher dosing or

more interference in the antibody assay from detectable serum levels of CNTO 1275 with higher dosing.

Table 8 Summary of antibody to CNTO 1275 status through the date the last subject completed Week 52; treated subjects randomized at Week 0

	CNTO 1275				
	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg	Combined
Subjects treated with CNTO 1275	123	120	255	255	753
Subjects with appropriate samples ^a	121	117	254	251	743
Subjects positive for antibodies to CNTO 1275 at any time ^{b,c}	6 (5.0%)	9 (7.7%)	18 (7.1%)	5 (2.0%)	38 (5.1%)
Titers					
1:10	1	3	6	1	11
1:20	3	1	4	0	8
1:40	0	2	3	1	6
1:80	0	1	1	0	2
1:160	1	1	1	0	3
1:320	1	1	2	1	5
1:640	0	0	0	2	2
1:2560	0	0	1	0	1
Subjects negative for antibodies to CNTO 1275 after last treatment ^{b,d}	70 (57.9%)	74 (63.2%)	122 (48.0%)	85 (33.9%)	351 (47.2%)
Subjects with undetectable antibody to CNTO 1275 status after last treatment ^{b,e}	45 (37.2%)	34 (29.1%)	114 (44.9%)	161 (64.1%)	354 (47.6%)

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

^b Denominator is subjects with appropriate samples.

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

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

^e Includes all subjects whose last sample could not be classified as negative due to potential interference from circulating active study agent, and excludes subjects who were positive at any time.

Among the remaining subjects, 351 (47.2%) subjects in the combined CNTO 1275 group were determined to be negative for antibodies to CNTO 1275 through Week 52, while 354 (47.6%) subjects in the combined CNTO 1275 group were undetectable or inconclusive for antibodies to CNTO 1275. The high percentage of subjects with detectable CNTO 1275 levels (who were classified as undetectable for antibodies to CNTO 1275) was expected given the majority of subjects received continuous dosing with CNTO 1275 through Week 52.

Reviewer's Comments: This data indicates that the sampling times for the antibody measurements did not allow for adequate wash-out period.

The timeframe for antibody development was evaluated by the applicant. Of the 23 antibody-positive subjects in the 45 mg and 90 mg groups:

- 10 subjects tested positive at Week 12.
- 9 subjects tested newly positive between Weeks 12 and 40.
- 4 subjects tested newly positive at Week 52.

Of the 15 antibody positive subjects in the placebo → 45 mg and placebo → 90 mg groups:

- 7 subjects tested positive between Weeks 12 and 40
- 8 subjects tested positive at Week 52.

These results suggest there is no fixed time for development of antibodies to CNTO 1275.

Impact of Weight on the Incidence of Antibodies to Study Agent:

Among subjects who weighed ≤ 100 kg at baseline, 11 (2.3 %) subjects were positive for antibodies to CNTO 1275. The proportions of subjects who were antibody positive and weighed ≤ 100 kg were similar across the 45 mg and 90 mg groups.

Among subjects who weighed > 100 kg at baseline, 27 (10.3 %) subjects were positive for antibodies to CNTO 1275. A higher proportion of subjects in the higher weight group were antibody positive compared with the lower weight group (10.3 % versus 2.3 %).

Among subjects who weighed > 100 kg at baseline, a greater proportion of subjects in the 45 mg group (18.4 %) tested positive for antibodies compared with the 90 mg group (2.2 %). A similar trend was observed for a higher rate of antibodies to CNTO 1275 in the combined 45 mg group compared with the combined 90 mg group (19 [14.5 %] subjects versus 8 [6.2 %] subjects). These results suggest that antibody rates are lower with 90 mg versus 45 mg. However, it should be noted that CNTO 1275 serum concentrations were generally higher in subjects in the lower weight group. Thus, the lower incidence of antibodies in the lower weight group may be a result of antibody assay interference from higher serum levels of CNTO 1275.

Reviewer's Comments: Data should be interpreted with caution due to inadequate wash-out period and assay interference by CNTO 1275.

Antibodies and PK

Antibodies to CNTO 1275 through Week 52 were generally associated with lower serum concentrations of CNTO 1275 through Week 28.

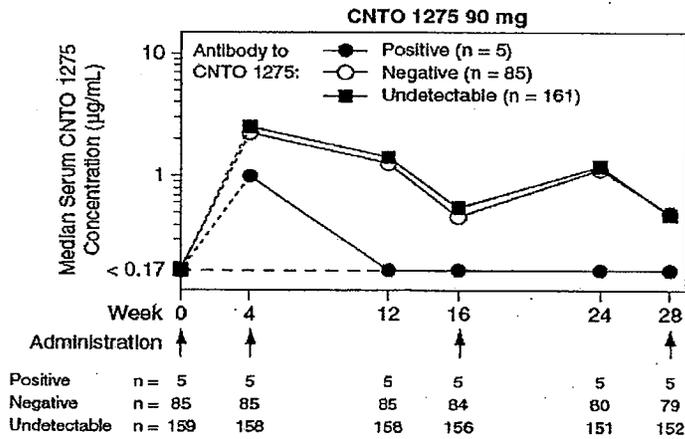
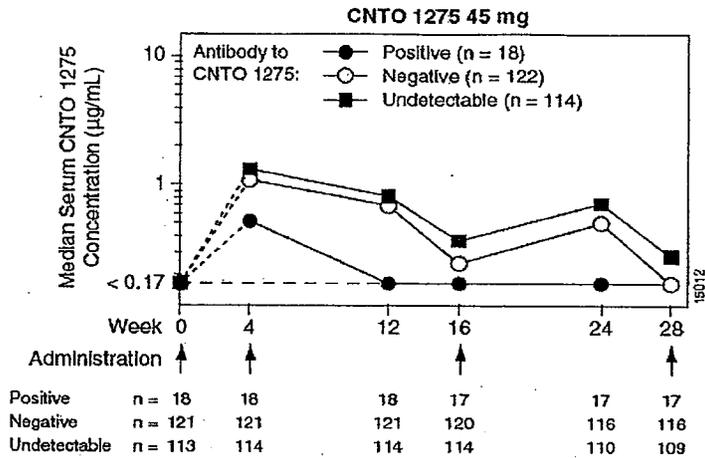


Figure 14 Median serum CNTO 1275 concentration (micrograms/mL) through Week 28 by antibody to CNTO 1275 status through Week 52; treated subjects who were randomized to CNTO 1275 at Week 0

Subjects who were positive for antibodies to CNTO 1275 maintained median serum levels of CNTO 1275 that were consistently lower than those in subjects who were negative for antibodies to CNTO 1275. As expected, due to the presence of serum CNTO 1275 concentrations that were > LOQ, subjects classified as inconclusive (undetectable) for antibodies to CNTO 1275 maintained median serum concentrations of CNTO 1275 that were consistently higher than those in subjects who were either positive or negative for antibodies to CNTO 1275.

Reviewer's Comments: Immunogenicity data should be interpreted with caution due to inadequate wash-out period, limitations of the antibody assay method due to interference from ustekinumab. In addition the high percentage of inconclusives does not allow for a true estimate of the incidence rate of positive immune response.

Pharmacokinetic Summary

- Serum CNTO 1275 concentrations were higher in the 90 mg group than the 45 mg group, with differences between the 2 groups showing dose proportionality.
- Steady state was achieved by Week 28. The median steady-state trough serum concentrations at Week 28 were 0.21 µg/mL (45 mg q12w) and 0.47 µg/mL (90 mg q12w).
- There was no evidence of accumulation in CNTO 1275 concentrations over time when given subcutaneously q12w.
- Subjects of higher weight (> 100 kg) had lower serum CNTO 1275 concentrations compared with subjects of lower weight (≤ 100 kg).

Antibodies to ustekinumab Summary

- The overall incidence of antibodies to CNTO 1275 through Week 52 was low with 38 (5.1%) subjects developing an immune response to CNTO 1275.
- The overall incidence of antibodies in the combined 45 mg group was higher than the combined 90 mg group (24 [6.4%] subjects versus 14 [3.8%] subjects).
- Among subjects who weighed > 100 kg, a higher rate of antibodies to CNTO 1275 was observed in the combined 45 mg group compared with the combined 90 mg group (19 [14.5%] subjects versus 8 [6.2%] subjects).
- Subjects who are positive for antibodies to CNTO 1275 exhibited median serum levels of CNTO 1275 that were consistently lower than those in subjects who were negative for antibodies to CNTO 1275. This finding should be interpreted with caution due to antibody assay interference from serum levels of CNTO 1275.

Reviewer's Comments; This reviewer does not concur with the applicant's conclusions for the antibodies to ustekinumab due to the limitations of the antibody assay method and the lack of adequate wash-out period incorporated into the sampling times for the antibody measurements.

Study # C0743T09:

Title of the study: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Evaluating the Efficacy and Safety of CNTO 1275 in the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis

Study Name: Phoenix 2

Principal/Coordinating Investigator: Prof. Kristian Reich, SCIderm GmbH, Stephansplatz 5, 20354 Hamburg, Germany

Study Centers: 70 investigative sites: 3 sites in Austria, 19 sites in Canada, 1 site in France, 10 sites in Germany, 2 sites in Switzerland, 3 sites in the United Kingdom, and 32 sites in the United States

Studied Period: 03 Mar 2006/26 Mar 2007

Phase of Development: 3

Objectives: The primary objective of this study was to evaluate the efficacy and safety of CNTO 1275 in the treatment of subjects with moderate to severe plaque psoriasis. Secondary objectives were to: (1) Evaluate dosing interval adjustment in subjects who inadequately respond to their starting dose regimen and (2) Evaluate the impact of CNTO 1275 on the quality of life.

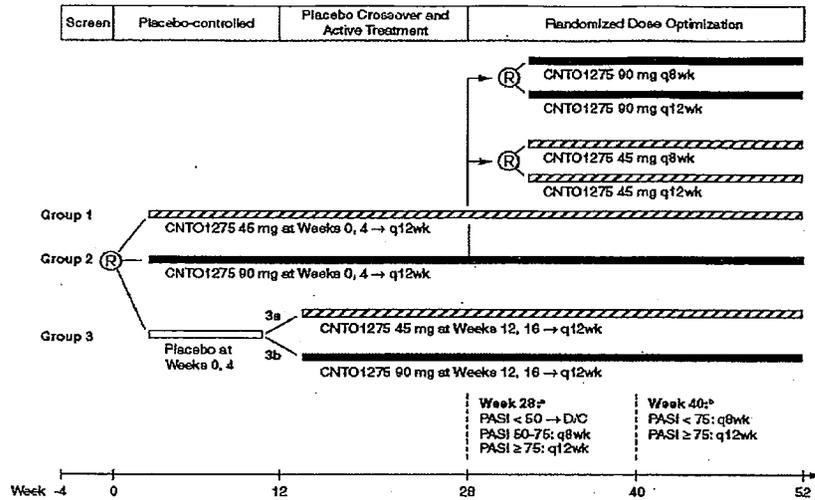
Methodology: This is a multicenter, randomized, placebo-controlled, double-blind, parallel, 3-arm study of SC injections of CNTO 1275 45 mg (Group 1), CNTO 1275 90 mg (Group 2), and placebo (Group 3) in subjects with moderate to severe plaque psoriasis.

The study consists of 4 study periods occurring over approximately 5 years (information only on portions 1 and 2 are provided in this report):

- A 12-week placebo-controlled,
- A subsequent 16-week placebo crossover and active treatment period,
- A 24-week dose schedule optimization period beginning at week 28,
- A long-term extension period begins at week 52 for a total of approximately 4 years

This report includes analyses from the first 2 of these 4 study periods, and includes all data available through Week 28, up to but not including, the Week 28 administration of study agent.

Study Design:



D/C = discontinued; PASI = Psoriasis Area and Severity Index; ⊕ = randomization; q8wk = every 8 weeks; q12wk = every 12 weeks
^a At Week 28, in Groups 1 and 2, PASI responders (PASI ≥ 75) continued q12wk dosing and partial responders were randomized to either q8wk or q12wk dosing.

In Group 3 only, PASI responders (PASI ≥ 75) began q12wk dosing and partial responders (PASI 50-75) began q8wk dosing. In all groups, nonresponders (PASI < 50) discontinued treatment but continued in the study.

^b At Week 40, among PASI responders (PASI ≥ 75) at Week 28 in all groups, partial responders (PASI 50-75) and nonresponders (PASI < 50) were adjusted to q8wk dosing and PASI responders (PASI ≥ 75) received q12wk dosing.

Figure 15: Study Design Overview

Number of Subjects (Planned and Analyzed): 1200 planned (400 subjects per group); 1230 subjects were randomized to treatment and analyzed for efficacy and for safety.

Diagnosis and Main Criteria for Inclusion: Men or women ages 18 years or older with moderate to severe plaque psoriasis who were candidates for systemic therapy or phototherapy and had a Psoriasis Area and Severity Index (PASI) ≥ 12, and at least 10% of their total body surface area (BSA) involved. Appropriate washout periods were specified for prior use of other biologics, investigational drugs, immunosuppressants, vaccines, and systemic or topical treatments that could affect psoriasis or PASI evaluations.

Test Product, Dose and Mode of Administration, Batch Number: 45 or 90 mg CNTO 1275 (0.5 or 1.0 mL, respectively) was administered by SC injection. Subjects randomized to the 45 or 90 mg CNTO 1275 groups were to receive CNTO 1275 at Weeks 0, 4, and 16. At Week 12, subjects randomized to placebo, were to receive 45 mg or 90 mg CNTO 1275 at Weeks 12 and 16. Two lots of CNTO 1275 (D05PE7427 and D05PE7428) were used.

Study agent was to be initially administered at the investigator site by an appropriately licensed and authorized health professional for the first 12 weeks (i.e., up to 2 doses). At Week 12 and at the discretion of the investigator and subject, and after appropriate training, study agent could have been self-administered at the investigative site by the

subject. All subjects were encouraged to self-inject by Week 52. Specific instructions for injection of study agent were supplied in the Study Reference Manual.

Duration of Treatment: First to last administration of study agent is 16 weeks of treatment; pharmacokinetic, efficacy and safety data were evaluated through Week 28, and antibodies to CNTO 1275 evaluated through Week 24.

Pharmacokinetics: Blood samples for the determination of serum CNTO 1275 concentration were collected at Weeks 0, 4, 12, 16, 24, and 28. At visits when study agent was scheduled, samples were collected just before the study agent was administered.

Immunogenicity: Serum samples were collected from all subjects at baseline, Weeks 12, and 24 to determine the incidence of antibodies to CNTO 1275. At visits when study agent was scheduled, samples were collected just before the study agent was administered.

Bioanalytical Methods:

Pharmacokinetics: Electrochemiluminiscent Immunoassay was used to determine serum CNTO 1275 concentrations. The LOQ of the method was 16.88 ng/mL (0.17 mcg/mL)

Immunogenicity: Analyses for the detection of antibodies to CNTO 1275 in human serum samples were performed using an enzyme immunoassay (EIA). Since CNTO 1275 can interfere with the detection or interpretation of an anti-CNTO 1275 antibody response, all samples evaluated for antibodies to CNTO 1275 were analyzed for CNTO 1275 concentrations. Subjects were defined as follows:

- Subjects were characterized as positive for antibodies to CNTO 1275 if any sample was positive for anti-CNTO 1275 antibodies, regardless of the presence or absence of CNTO 1275 in the samples.
- Subjects were characterized as negative for antibodies to CNTO 1275 if the last serum sample did not contain measurable CNTO 1275 and if antibodies to CNTO 1275 were not detected in all samples evaluated after CNTO 1275 administration.
- Subjects were characterized as undetectable or inconclusive if antibodies to CNTO 1275 were not detected in all samples and there were measurable concentrations of CNTO 1275 present in the last serum sample(s) evaluated after CNTO 1275 administration.

Efficacy: The primary endpoint was the proportion of subjects who achieved PASI 75 response at Week 12. Efficacy assessments included PASI and Physician's Global Assessment (PGA). In addition, the relationship between serum CNTO 1275 concentration and efficacy was examined. The impact of antibody to CNTO 1275 status on efficacy and safety was explored.

Safety: Safety was assessed by 1) AEs and serious AEs (SAEs) that may have occurred at and between each of the evaluation visits; 2) tuberculosis (TB) evaluation; 3) changes in routine laboratory analyses (hematology and chemistry); 4) evaluation of fasting glucose, hemoglobin A1c, C-reactive protein (CRP), and D-dimer at selected time points.

Statistical Methods: Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables were used to summarize most data.

Results

Study Population: A total of 1230 subjects, (68.3% male, 91/7 % Caucasian), and the median age and body weight of subjects was 47.0 years (range: 18 to 86 years) and 88.6 kg (range; 37.4 kg to 195.1 kg), respectively. Baseline disease characteristics indicated a population of subjects with moderate to severe psoriasis. The mean duration of psoriasis was 18.5 years. The population spanned moderate to severe psoriasis, with a median BSA of 20.0% and a median PASI score of 17.5. One thousand twelve hundred and twelve (1212) subjects were analyzed for the pharmacokinetics of CNTO 1275.

Pharmacokinetic:

Serum CNTO 1275 Concentration-Time Profiles:

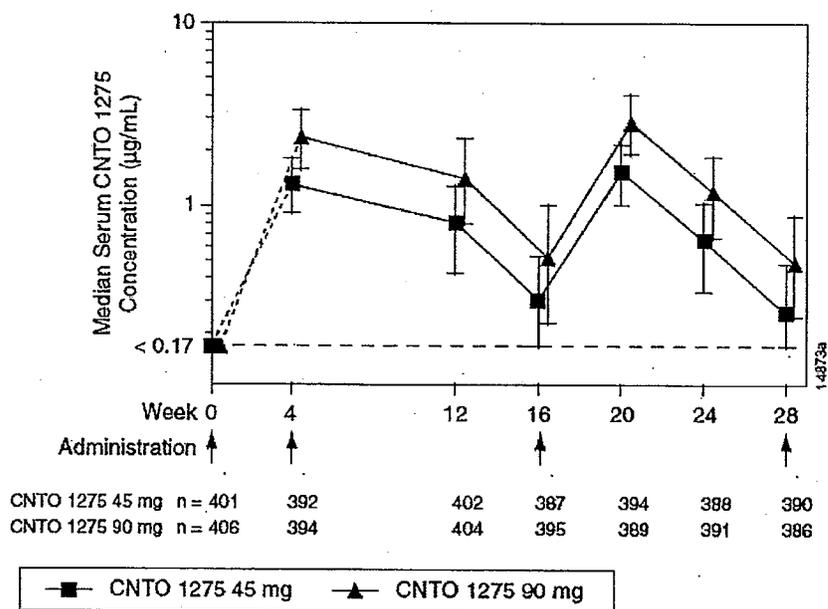


Figure 16 Median and IQ range of serum CNTO 1275 concentration (µg/mL) through Week 28; treated subjects randomized to CNTO 1275 at Week 0

At each sampling time point from Week 4 through Week 28, serum CNTO 1275 concentrations were higher in the 90 mg group than the 45 mg group, with the difference

between the 2 groups showing approximate dose proportionality. At weeks 4, 12, 16, and 28 the median trough serum concentrations of CNTO 1275 were 0.31 mcg/mL (45 mg) and 0.52 mcg/mL (90 mg).

In the placebo-45 mg and placebo-90 mg groups, the median serum concentrations of CNTO 1275 observed at Weeks 16, 24, and 28 were similar to those levels observed at Weeks 4, 12, and 16 in subjects in the 45 mg and 90 mg groups.

Attachment 2.1 Summary of serum CNTO 1275 concentrations (micrograms/mL) through Week 28 by visit; subjects treated with CNTO 1275

	CNTO 1275			
	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg
Subjects treated with CNTO 1275	197	195	409	411
Week 0				
n	194	195	401	406
Mean ± SD	0.01 ± 0.128	0.00 ± 0.000	0.00 ± 0.028	0.00 ± 0.041
Median	0.00	0.00	0.00	0.00
IQ range	(0.00, 0.00)	(0.00, 0.00)	(0.00, 0.00)	(0.00, 0.00)
Range	(0.0, 1.8)	(0.0, 0.0)	(0.0, 0.5)	(0.0, 0.8)
Week 4				
n	195	193	392	394
Mean ± SD	0.01 ± 0.082	0.00 ± 0.018	1.40 ± 0.748	2.55 ± 1.342
Median	0.00	0.00	1.31	2.39
IQ range	(0.00, 0.00)	(0.00, 0.00)	(0.91, 1.84)	(1.59, 3.35)
Range	(0.0, 1.1)	(0.0, 0.3)	(0.0, 4.1)	(0.0, 7.2)
Week 12				
n	195	192	402	404
Mean ± SD	0.01 ± 0.124	0.00 ± 0.027	0.93 ± 0.866	1.67 ± 1.202
Median	0.00	0.00	0.81	1.42
IQ range	(0.00, 0.00)	(0.00, 0.00)	(0.43, 1.29)	(0.80, 2.33)
Range	(0.0, 1.7)	(0.0, 0.4)	(0.0, 12.5)	(0.0, 6.3)
Week 16				
n	191	190	387	395
Mean ± SD	1.32 ± 0.733	2.57 ± 1.450	0.35 ± 0.344	0.69 ± 0.656
Median	1.13	2.34	0.31	0.52
IQ range	(0.81, 1.80)	(1.47, 3.54)	(0.00, 0.53)	(0.23, 1.02)
Range	(0.0, 3.9)	(0.0, 6.4)	(0.0, 2.0)	(0.0, 3.5)
Week 20				
n	189	192	394	389
Mean ± SD	1.86 ± 1.000	4.06 ± 2.520	1.67 ± 0.961	3.23 ± 1.841
Median	1.81	3.72	1.54	2.86
IQ range	(1.14, 2.36)	(2.19, 5.32)	(1.02, 2.19)	(1.93, 4.11)
Range	(0.0, 5.9)	(0.0, 14.2)	(0.0, 5.9)	(0.0, 12.4)
Week 24				
n	190	189	388	391
Mean ± SD	0.80 ± 0.628	1.73 ± 1.201	0.74 ± 0.556	1.38 ± 0.984
Median	0.62	1.49	0.65	1.20
IQ range	(0.36, 1.12)	(0.79, 2.45)	(0.34, 1.03)	(0.67, 1.86)
Range	(0.0, 3.9)	(0.0, 5.7)	(0.0, 3.9)	(0.0, 5.8)
Week 28				
n	190	188	390	386
Mean ± SD	0.31 ± 0.350	0.79 ± 0.734	0.31 ± 0.328	0.64 ± 0.638
Median	0.25	0.59	0.26	0.49
IQ range	(0.00, 0.47)	(0.27, 1.17)	(0.00, 0.48)	(0.25, 0.89)
Range	(0.0, 1.6)	(0.0, 3.7)	(0.0, 1.8)	(0.0, 3.7)

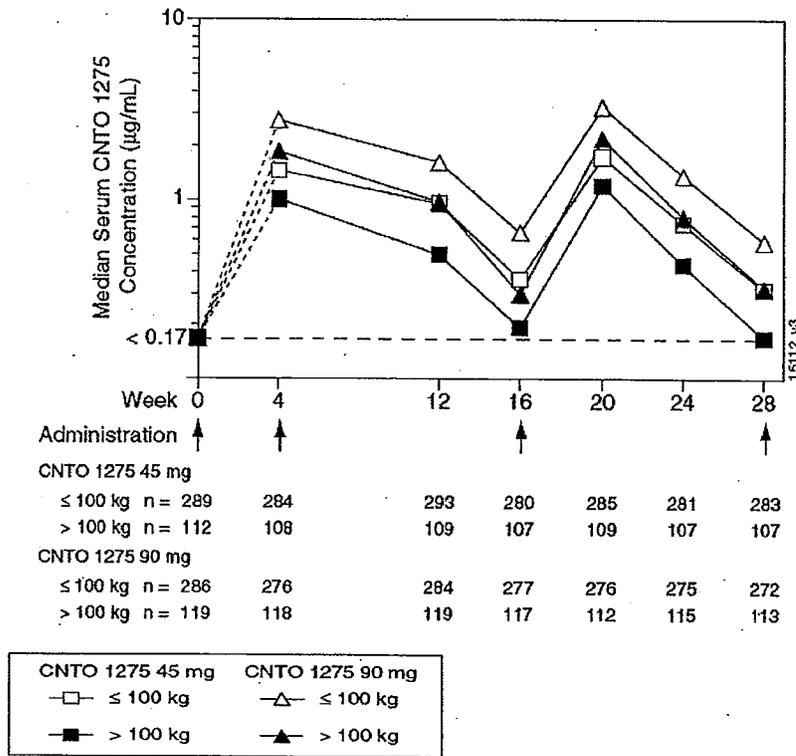
Serum Concentrations below LOQ:

The proportion of subjects with concentrations below the LOQ was higher at each visit in the 45 mg group compared with that in the 90 mg group. At week 28, the percent of subjects with trough serum CNTO 1275 concentrations below the LOQ was 38.7 % (45 mg) and 21.2 % (90 mg).

Impact of Weight on Serum Concentrations:

Because dose-response in efficacy was most apparent in subjects > 100 kg, the impact of weight on serum concentrations was examined by classifying subjects' baseline weight into 2 groups: ≤ 100 kg and > 100 kg.

Figure 17 Median serum CNTO 1275 concentrations (µg/mL) through Week 28 by body weight (≤ 100 kg, > 100 kg); treated subjects randomized to CNTO 1275 at Week 0



Serum CNTO 1275 concentrations appeared to be impacted by weight.

- Subjects of higher weight (> 100 kg) had lower median serum CNTO 1275 concentrations compared with subjects of lower weight (\leq 100 kg).
- Within each dose (i.e. 45 mg and 90 mg), the median trough serum CNTO 1275 concentrations at all the sampling time points in subjects with weights > 100 kg were generally lower (30-50 %) compared with those in subjects of lower weight (\leq 100 kg).
- Across doses, the median trough serum concentrations of CNTO 1275 in subjects of higher weight (> 100 kg) in the 90 mg group were comparable to those in subjects of lower weight (\leq 100 kg) in the 45 mg group.

Immunogenicity:

The overall incidence of antibodies to CNTO 1275 through Week 24 was 2.8 % (33 out of 1198 subjects). The proportion of subjects who were positive for antibodies to CNTO 1275 was higher in the 45 mg group (4.4 %) than the 90 mg group (2.2 %). However, this finding was not observed in the placebo to 45 mg group (2.6 %) compared with the placebo to 90 mg group (0.5 %). However, when combined, a trend was observed for a higher proportion of subjects in the combined 45 mg group to be positive for antibodies to CNTO 1275 compared with the combined 90 mg group (23 [3.9 %] subjects versus 10 [1.7%] subjects). The higher rate of antibodies to CNTO 1275 in the 45 mg group was apparent regardless of subject's weight (\leq 100 kg or > 100 kg). Subjects classified as undetectable for antibodies to CNTO 1275 maintained median serum concentrations of CNTO 1275 that were consistently higher than those in subjects either positive or negative for antibodies to CNTO 1275. Lower immunogenicity in the 90 mg group may be due to higher dosing or more interference in the antibody assay from detectable serum levels of CNTO 1275 with higher dosing.

Among the remaining subjects, 90 (7.5%) subjects in the combined CNTO 1275 group were determined to be negative for antibodies to CNTO 1275 through Week 24, while 1075 (89.7%) subjects in the combined CNTO 1275 group were undetectable or inconclusive to CNTO 1275. The high percentage of subjects with detectable CNTO 1275 levels (who were classified as undetectable for antibodies to CNTO 1275) was expected, given the majority of subjects received their last administration of CNTO 1275 at Week 16, only 8 weeks prior to the end of the 24 week study period.

Reviewer's Comments: As noted by applicant above sampling times did not allow for adequate wash-out period of CNTO 1275.

An evaluation of the time-frame for antibody development indicated that there is no fixed time for the development of antibodies to CNTO 1275.

Table 7 Summary of antibody to CNTO 1275 status through Week 24; subjects treated with CNTO 1275

	CNTO 1275				
	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg	Combined
Subjects treated with CNTO 1275	197	195	409	411	1212
Subjects with appropriate samples ^a	192	194	405	407	1198
Subjects positive for antibodies to CNTO 1275 at any time ^{b,c}	5 (2.6%)	1 (0.5%)	18 (4.4%)	9 (2.2%)	33 (2.8%)
Titers					
1:10	1	1	1	1	4
1:20	1	0	2	3	6
1:40	2	0	1	1	4
1:80	0	0	4	2	6
1:160	1	0	0	1	2
1:320	0	0	3	1	4
1:640	0	0	4	0	4
1:1280	0	0	2	0	2
1:5120	0	0	1	0	1
Subjects negative for antibodies to CNTO 1275 after last treatment ^{b,d}	16 (8.3%)	14 (7.2%)	41 (10.1%)	19 (4.7%)	90 (7.5%)
Subjects with undetectable antibody to CNTO 1275 status after last treatment ^{b,e}	171 (89.1%)	179 (92.3%)	346 (85.4%)	379 (93.1%)	1075 (89.7%)

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

^b Denominator is subjects with appropriate samples.

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

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

^e Includes all subjects whose last sample could not be classified as negative due to potential interference from circulating active study agent, and excludes subjects who were positive at any time.

Impact of Weight on Incidence of Antibodies to Study Agent:

Among subjects who weighed ≤ 100 kg at baseline, 15 (1.8 %) subjects were positive for antibodies to CNTO 1275. Among subjects who weighed ≤ 100 kg at baseline, a greater proportion of subjects in the 45 mg group (92.0 %) tested positive for antibodies compared with the 90 mg group. In the placebo to 45 mg group, the proportion of subjects positive for antibodies to CNTO 1275 was higher compared with the placebo to 90 mg group (3.8 % versus 0.0 %). Similar trend was observed for the combined group.

Among subjects who weighed > 100 kg at baseline, 18 (5.3 %) subjects were positive for antibodies to CNTO 1275. A higher proportion of subjects in the higher weight group was antibody positive compared with the lower weight group (5.3 % versus 1.8 %).

Among subjects who weighed > 100 kg at baseline, a greater proportion of subjects in the 45 mg group (10.9 %) tested positive for antibodies compared with the 90 mg group (4.2 %). In the placebo to 45 mg group, the proportion of subjects positive for antibodies to CNTO 1275 was lower compared with the placebo to 90 mg group (0.0 % versus 1.9 %). A similar trend was observed for a higher rate of antibodies to CNTO 1275 in the combined 45 mg group compared with the combined 90 mg group (12 [7.1%] subjects versus 6 [3.5%] subjects). These results suggest that antibody rates are lower with 90 mg versus 45 mg. However, it should be noted that CNTO 1275 serum concentrations were generally higher in subjects in the lower weight group. Thus, the lower incidence of antibodies in the lower weight group may be a result of antibody assay interference from higher serum levels of CNTO 1275.

Antibodies and PK

Antibodies to CNTO 1275 through Week 24 were generally associated with lower serum concentrations of CNTO 1275 through Week 28. Subjects who were positive for antibodies to CNTO 1275 maintained median serum levels of CNTO 1275 that were consistently lower than those in subjects who were negative or undetectable for antibodies to CNTO 1275. Subjects classified as undetectable for antibodies to CNTO 1275 maintained median serum concentrations of CNTO 1275 that were consistently higher than those in subjects either positive or negative for antibodies to CNTO 1275. CNTO 1275 concentrations \geq LLOQ at the time of antibody assessment, thus it is not surprising that antibody-positive or negative subjects had lower CNTO 1275 concentrations relative to those subjects with undetectable antibody status.

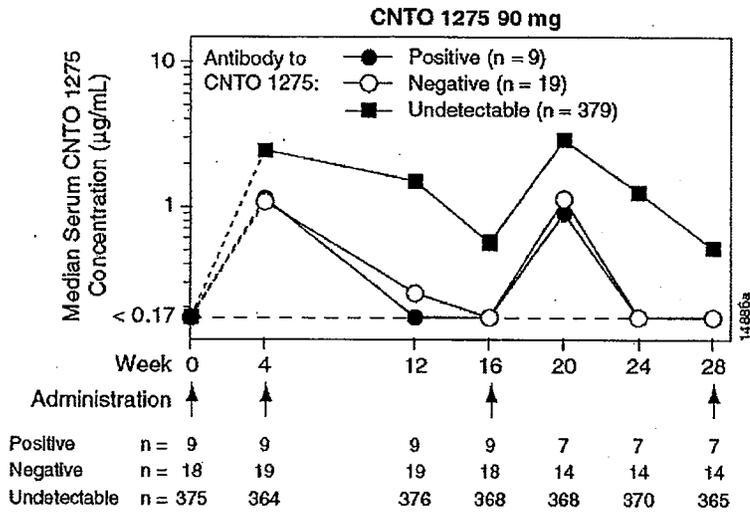
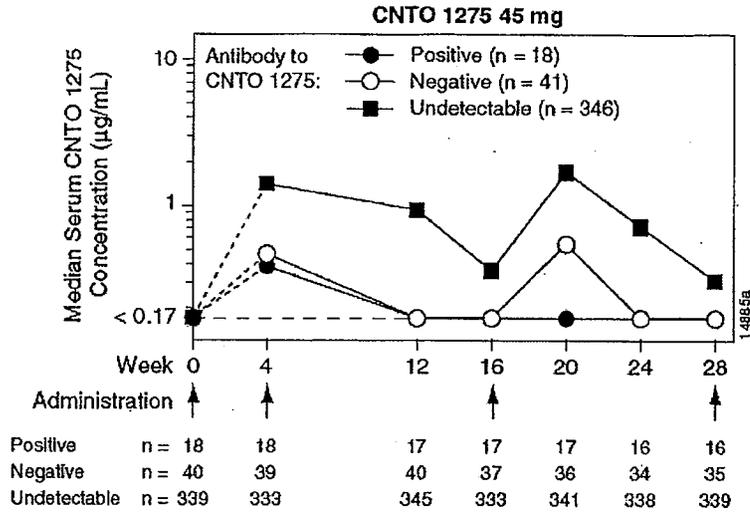


Figure 6 Median serum CNTO 1275 concentration ($\mu\text{g/mL}$) through Week 28 by antibody to CNTO 1275 status through Week 24; treated subjects who were randomized to CNTO 1275 at Week 0

Relationship between efficacy and PK and AB status

Clinical response was generally associated with serum CNTO 1275 levels. Subjects with higher clinical response (as measured by PASI response) had higher median serum concentrations of CNTO 1275 than those with lower clinical response.

The low incidence of antibody-positive subjects precludes definitive conclusions on the impact of antibody status on clinical response. Subjects who were positive for antibodies to CNTO 1275 tended to have lower clinical efficacy, however antibody positivity does not preclude a clinical response.

Pharmacokinetic Summary

- At each sampling timepoint from Week 4 through Week 28, serum CNTO 1275 concentrations were higher in the 90 mg group than the 45 mg group, with the difference between the 2 groups showing dose proportionality.
- The median trough serum levels at Week 28 were 0.26 µg/mL (45 mg) and 0.49 µg/mL (90 mg).
- There was no evidence of accumulation in CNTO 1275 concentrations over time when given subcutaneously q12w.
- Serum CNTO 1275 concentrations appeared to be impacted by weight:
 - Across doses, the median trough serum concentrations in subjects of higher weight (> 100 kg) in the 90 mg group were comparable to those in subjects of lower weight (≤ 100 kg) in the 45 mg group.
 - Within each dose, the median trough serum concentrations in subjects of higher weight (> 100 kg) were generally 30% to 50% lower compared with those in subjects of lower weight (≤ 100 kg).

Antibodies to Study Agent Summary

The overall incidence of antibodies to CNTO 1275 through Week 24 was low with 33 (2.8%) subjects developing antibodies to CNTO 1275. Antibody responses were predominantly of low titer. Observations based on the antibody-positive subjects are:

- The overall incidence of antibodies in the combined 45 mg group was higher than the 90 mg group (23 [3.9%] subjects versus 10 [1.7%] subjects).
- The higher rate of antibodies to CNTO 1275 in the 45 mg group was apparent regardless of subject's weight (≤ 100 kg or > 100 kg).
- Subjects classified as undetectable for antibodies to CNTO 1275 maintained median serum levels of CNTO 1275 that were consistently higher than those in subjects either positive or negative for antibodies to CNTO 1275.
- The low incidence of antibody-positive subjects and the high number of inconclusives precludes definitive conclusions on the impact of antibody status on clinical response. Subjects who were positive for antibodies to CNTO 1275 tended to have lower clinical efficacy, however antibody positivity does not preclude a clinical response.

Reviewer's Comments: Immunogenicity data should be interpreted with caution due to the limitations of the assay method, inadequate wash-out period and the high percentage of subjects that were classified as inconclusives.

Summary of Ustekinumab Immunogenicity Across Studies

The applicant evaluated the incidence of antibodies to ustekinumab across all studies, and their relationship to the pharmacokinetics of ustekinumab. In addition, all subjects positive for antibodies to ustekinumab in Phase 1 and Phase 2 were assessed for the potential of these antibodies to CNTO 1275 to neutralize CNTO 1275's ability to inhibit the functional activity of its target (IL-12/IL-23 p40).

Reviewer's Comments:

The applicant stated that subjects who are positive for antibodies to CNTO 1275 in Phase 3 will be tested for neutralizing antibodies to CNTO 1275, and these data will be provided in a future submission. Analyses of the relationships of antibody status to safety and efficacy measures have also been performed, and details of these relationships are provided in the clinical review.

Antibodies to ustekinumab were analyzed using a bridging enzyme immunoassay (EIA) to detect and characterize antibodies to CNTO 1275. This assay method was reviewed by the product reviewer. The product reviewer reported that one important limitation of the assay used to assess for antibodies to ustekinumab is the potential for assay interference by the ustekinumab itself. Thus, a true determination of a subject's antibody to ustekinumab status can only occur after sufficient time has passed to allow a subject to clear ustekinumab ("wash-out" period). This is more of a challenge for analyzing the immune response to ustekinumab which has along half-life and continuous exposure.

The applicant stated that the concern for assay interference by ustekinumab in the immune response assay has been addressed in the C0379T04 Phase 2 study, in which psoriasis subjects were administered a limited number (1 to 5 doses) of SC administrations, and then followed through 52 weeks to allow antibody assessment after an adequate wash-out period.

Incidence of Antibodies to Ustekinumab in subjects with Psoriasis

In 2 Phase 1 studies in psoriasis subjects (C0379T01 and C0379T02), the incidence of antibodies was 1 of 18 subjects (5.6%) and 1 of 17 subjects (5.9%), respectively. The incidence of antibodies to CNTO 1275 in the Phase 2 and Phase 3 psoriasis studies ranged from 1.7% to 6.4% (with a combined overall incidence of antibodies to CNTO 1275 in the 2 Phase 3 studies of 3.7% (83 of 2234).

In the C0379T04 Phase 2 psoriasis study, subjects were treated with single or multiple doses of CNTO 1275 and were followed up to 52 weeks allowing time for the elimination of detectable serum CNTO 1275 levels. In this study, ustekinumab was administered as

SC from Weeks 0-20 and the last visits assessed for antibodies was Week 52. See table below for a summary of the incidence of antibodies observed in study C037904; Through Week 52, 4.1% of subjects developed antibodies to CNTO 1275. The majority of the remaining subjects (85.3%) were negative for antibodies to CNTO 1275, and the remaining subjects (10.6%) were inconclusive at the last visit evaluated. Thus, allowing time for the elimination of detectable serum CNTO 1275 levels in the majority of subjects did not result in a substantially higher proportion of subjects with antibodies to CNTO 1275 even following multiple doses. At Week 36, 114 subjects (38.9%) were inconclusive, and 83 of these subjects became antibody negative at Week 52; there were no new antibody positive subjects observed.

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

Incidence of Antibodies to CNTO 1275 in Healthy Subjects

One study (C0743T11) was completed in healthy adult male subjects. In this single dose study, 1 of 29 (3.4%) subjects was positive for antibodies to CNTO 1275

Neutralizing Antibodies (NABs) to CNTO 1275

A cell-based neutralizing antibody (NAB) bioassay was developed to characterize whether antibodies to CNTO 1275 detected in the EIA assay would be able to neutralize the biological effects of CNTO 1275 in vitro. In the Phase 1 and Phase 2 studies, baseline and EIA positive samples from antibody positive subjects were assessed for CNTO 1275 neutralizing potential

Out of 13 EIA positive subjects (SC administration) from Phase 1 and Phase 2 studies in psoriasis (C0379T02, C0379T04), 9/13 (69.2%) were positive for NABs. This suggests that the antibodies are able to neutralize the bioreactivity of ustekinumab in vitro. The applicant stated that the EIA positive subjects that were not NAB positive in general, had low titer EIA antibody responses of $\leq 1:40$ titer and probably could not be characterized in the NAB assay due to the lower assay sensitivity of NAB assay compared with the EIA assay. The non-neutralizing CNTO 1275 antibody responses are unlikely to represent antibody responses directed toward a different (non-neutralizing) epitope on CNTO 1275, but are more likely attributable to differences in the sensitivity of the EIA and NAB assays.

Table: Summary of psoriasis subjects positive for neutralizing antibodies to Ustekinumab in the Phase 1 and 2 Clinical Studies

Study	Study Phase	Number of subjects with appropriate samples	# of EIA+ Subjects	NAb Incidence in EIA+ Subjects
C0379T02	1	18	1 (5.6%)	1/1 (100%)
C0379T04	2	293	12 (4.1%)	8/12 (67%)
Total		311	13 (4.2 %)	9/13 (69.2%)

Impact of Antibody incidence on Efficacy and Safety:

There was a tendency for subjects who were positive for antibodies to CNTO 1275 to be less likely to achieve a PASI 75 response than those subjects who were negative for antibodies to CNTO 1275. However, since the true incidence rate of the antibodies of ustekunimab cannot be determined from the limited data provided the effect of antibody status on efficacy and safety is unknown at this time. Please see clinical review for further details.

Table 8 Summary of incidence of antibodies to CNTO 1275 in subjects in Phase 2 and Phase 3 studies in psoriasis					
Dose Groups ^a	Subjects treated	Subjects with appropriate samples ^b	Status for Antibodies to CNTO 1275		
			Positive	Negative	Undetectable ^c
C0379T04^d					
Overall	301	293	12 (4.1%)	250 (85.3%)	31 (10.6%)
45 mg	63	60	3 (5.0%)	53 (88.3%)	4 (6.7%)
90 mg	113	111	4 (3.6%)	96 (86.5%)	11 (9.9%)
45 mg wk x 4	63	61	3 (4.9%)	53 (86.9%)	5 (8.2%)
90 mg wk x 4	62	61	2 (3.3%)	48 (78.7%)	11 (18.0%)
C0743T08^e					
Overall	753	743	38 (5.1%)	351 (47.2%)	354 (47.6%)
45 mg dosing	378	375	24 (6.4%)	192 (51.2%)	159 (42.4%)
90 mg dosing	375	368	14 (3.8%)	159 (43.2%)	195 (53%)
C0743T09^f					
Overall	1212	1198	33 (2.8%)	90 (7.5%)	1075 (89.7%)
45 mg dosing	606	597	23 (3.9%)	57 (9.5%)	517 (86.6%)
90 mg dosing	606	601	10 (1.7%)	33 (5.5%)	558 (92.8%)
Total	2266	2234	83 (3.7%)	691 (30.9%)	1460 (65.4%)
^a Indicated dosing for C0743T08 and C0743T09 was multiple doses; dose groups include all subjects who received CNTO 1275 at any time. ^b Subjects with appropriate samples had one or more samples obtained after their first study agent administration. ^c C0379T04 used the term inconclusive. A terminology change to "undetectable" was instituted for the Phase 3 studies (C0743T08 and C0743T09) ^d Last active injection: Weeks 0-20; Last visit assessed for antibodies: Week 52 ^e Last active injection: Weeks 28-48; Last visit assessed for antibodies: Week 52 ^f Last active injection: Week 16; Last visit assessed for antibodies: Week 24					

Bioanalytical Methods:

Serum CNTO 1275 Concentrations:

The bioanalytical methods used to determine the serum CNTO 1275 concentrations in the clinical studies were an enzyme-linked immunosorbant assay (ELISA) and an electrochemiluminescent immunoassay (ECLIA). The ELISA method was used for the Phase 1 (C0379T01 and C0379T02) and the Phase 2 (C0379T04) studies. The ECLIA method was used for the Phase 1 (C0743T11) and the Phase 3 (C0743T08 and C0743T09).

Enzyme-linked Immunosorbant Assay (ELISA) Method # CP2001V-009 for CNTO 1275 Concentration in Serum:



b(4)

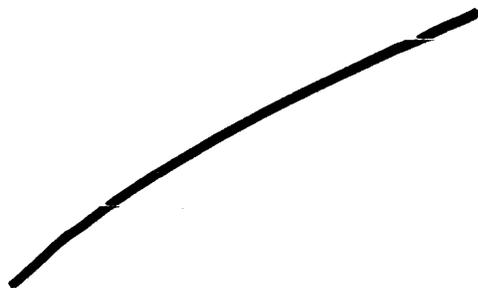
Table 9: Validation of the Analytical Method:

Method	Enzyme-linked Immunosorbant Assay (ELISA)
Compound	CNTO 1275
Matrix	Human Serum
Accuracy (% Nominal)	
<i>Intra-assay</i>	89.8 % to 102.9%
<i>Inter-assay</i>	84.4 % to 101.1 %
Precision (% CV)	
<i>Intra-assay</i>	4.7% to 7.1 %
<i>Inter-assay</i>	3.7 % to 11.3 %
Standard curve range	8.44 ng/mL to 270 ng/mL (%CV = 2.9 to 12.1 %, Accuracy = 91.1 to 101.8 %)
Sensitivity (LOQ)	8.44 ng/mL
Specificity	Demonstrated with 3 antibodies specific for other antigens in the presence and absence of CNTO 1275. These 3 antibodies did no interfere with the detection of CNTO 1275, nor were they recognized in the CNTO 1275 assay.

Stability of CNTO 1275 in Human Serum	CNTO 1275 was demonstrated to be stable in human serum following three freeze/thaw cycles. The mean (SD) recovery after 1, 2, or 3 freeze (-70° C) – thaw (37° C) cycles was 97.3 (5.4) %, 95.6 (6.5) % and 100.2 (7.8) %, respectively. Stability@ -20° C for 40 days was also demonstrated.
Conclusion	Method validation is acceptable

Electrochemiluminiscent Immunoassay (ECLIA) Method # CP2007V-001 for CNTO 1275 Concentration in Serum:

Assay Method:



b(4)

Table 10: Analytical Method and Validation:

Method	Electrochemiluminescent Immunoassay (ECLIA)
Compound	CNTO 1275
Matrix	Human Serum
Accuracy (% Bias) <i>Between-Day</i>	3.3 % to 5.3 %
Precision (% CV) <i>Between-Day</i>	12.0% to 14.8 %
Standard curve range	16.88 ng/mL - 1080.00 ng/mL (%CV = 3.85 to 13.58 % and % Bias = -1.63 to 9.42)
Sensitivity (LOQ)	16.88 ng/mL (0.17 mcg/mL) (% CV=11.1% and % Bias =9.42% for N=82)

Specificity	Antibodies to CNTO 1275 were shown to compete with the reagent antibodies for binding to CNTO 1275. This may result in either lower values for the measured amount of CNTO 1275, or reduction of values below the LOQ, thereby reducing the accuracy and apparent level of detection for the method.
Recovery (Mean %)	71.8 to 140.7 % (Mean = 96.2 %) Decreased recovery (2.95% to 58.31%) of CNTO 1275 was demonstrated in immune response positive samples. The extent of the decrease in recovery directly correlated with the level of immune response as indicated by the sample titer.
Stability of CNTO 1275 in Human Serum	CNTO 1275 was demonstrated to be stable in human serum following storage @ room temperature for up to 48 hours, and @ 4° C for up to 7 weeks and -70° C for 17 months
Conclusion	Method validation is acceptable.

Comparison of the ELISA and ECLIA Bioanalytical Methods:

The applicant stated that using QCs and incurred study serum samples to compare both methods, it was found that the ELISA could overestimate serum concentrations of CNTO 1275 because the majority of the concentrations obtained by ELISA method were consistently higher than those obtained by the ECLIA method.

Back-calculated concentrations of 30 QC samples ranging from 60 to 1,000,000 ng/mL were used for the determination of accuracy for the ELISA and ECLIA methods. The percent recovery (observed concentration divided by the nominal concentration multiplied by 100) of the QC samples analyzed in the ELISA ranged from 93.85 to 203.32 % with a mean recovery of 123.32 %. In the ECLIA, the percent recovery ranged from 71.84 to 140.71 % with a mean recovery of 96.2 %. In general the QC samples had a high recovery in the ELISA compared to the recovery obtained with the ECLIA.

Bioanalytical Methods for the Detection and Characterization of Antibodies to CNTO 1275 in Serum:

An enzyme immunoassay (EIA) method was developed to detect antibodies to CNTO 1275 in human serum samples. Human serum samples from clinical studies identified as containing antibodies to CNTO 1275 were further characterized for the ability of those antibodies to neutralize the bioactivity of CNTO 1275 using a cell-based assay.

Briefly, antibodies to CNTO 1275 were determined using an antigen bridging enzyme immunoassay (EIA), an assay that measures immune responses from any species. Several stages of testing were required for this assay. First, the sera were screened at a 1:10 dilution and the optical densities (ODs) of the test samples were compared with an assay cut-off OD. The assay cut-off OD (0.131) was set by evaluating serum samples from

various populations of individuals not previously exposed to CNTO 1275 (adult and pediatric Crohn's disease, rheumatoid arthritis, psoriasis, multiple sclerosis and normal volunteers) and then calculating a grand mean OD plus 3 standard deviations (SDs). In addition, the baseline and post-treatment sample ODs were compared for a 2-fold OD increase.

Potentially positive samples and the subject's pretreatment sample were tested for titer. Specificity of the response for CNTO 1275 was assessed by the addition of soluble CNTO 1275. Binding was determined to be specific for CNTO 1275 if the sample OD was reduced by at least 50% following preincubation with soluble CNTO 1275. Positive and negative control samples were included in each assay run. Designation of a specific serum sample as having a positive immune response required an OD result in excess of the cut-off in the screening assay, as well as in the 1:10 dilutions included for either the titer or inhibition assays. Additionally, OD values must have decreased with increasing sample dilutions in the titer assay, and following preincubation with soluble CNTO 1275 in the inhibition assay. Subject samples designated as negative for an immune response to CNTO 1275 must have had an OD value less than the 0.131 cut-off value in the screening assay, and must not have had a CNTO 1275 serum concentration in excess of limits of quantification in the assay ($> 0.09 \mu\text{g/mL}$). Samples for which the screening results were less than the cut-off value, and CNTO 1275 was present in the serum, were designated as immune response-inconclusive.

Reviewer's Comments: These assay methods were reviewed by the product reviewer. Therefore, this reviewer did not review them again. Please refer to product review for further details on the validation method. Include product reviewer's conclusions.

Pharmacodynamic Analytical Methods:

Pharmacodynamic (PD) analyses including histological assessments, gene expression, concentrations of serum cytokines and chemokines, and flow cytometric analysis of T-lymphocyte cell surface markers and functional analyses were used to better understand the mechanism of action of CNTO 1275. The assays used for these different analyses were not developed and validated by the applicant they were basically commercial kits or standard methods.

Reviewer's Comments: These studies were not reviewed in detail because they were only used to better understand the mechanism of action of CNTO 1275.

Additional Information

Attachment 7.3: List of Concomitant Medications and Number of Subjects on Concomitant Medications in Studies C0743T09 and C0743T08

Concomitant Medications	Code	No. of Subjects
Acetylsalicylic Acid	1	253
Amlodipine	2	69
Amoxicillin	3	82
Atenolol	4	61
Atorvastatin	5	140
Elecoxib	6	57
Citalopram	7	46
Diphenhydramine	8	88
Hydrochlorothiazide	9	110
Hydroxyzine	10	75
Ibuprofen	11	337
Influenza Vaccine	12	106
Isoniazid	13	67
Levothyroxine	14	119
Lisinopril	15	74
Medinix	16	66
Metformin	17	153
Metoprolol	18	57
Naproxen	19	136
Omeprazole	20	60
Panadeine CO	21	70
Paracetamol	22	357
Ramipril	23	76
Salbutamol	24	80
Azithromycin	25	54
Cefalexin	26	57
Hydrocortisone	27	43
Vicodin	28	54

4.3 Consult Reviews

Pharmacometrics Review: [See Attached]

Pharmacogenomics Review: [See Attached]

4.4 Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology				
<i>Biological License Application Filing and Review Form</i>				
<i>General Information about the Submission</i>				
	Information		Information	
BLA Number	125261/0	Brand Name	Stelera (pending)	
OCPB Division (I, II, III)	DCP3	Generic Name	Ustekinumab	
Medical Division	HFD-540	Drug Class	Human Interleukin 12 and 23 antagonist	
Primary Reviewer	Abi Adebowale	Indication(s)	Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.	
Secondary Reviewer	Jang-IK Lee	Dosage Form and Strengths	45 mg/0.5 mL in a single-use glass vial 90 mg/1.0 mL in a single-use glass vial	
Letter Date	November 28 th , 2007	Dosing Regimen	<ul style="list-style-type: none"> For patients weighing ≤ 100 kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by dosing every 12 weeks. For patients weighing > 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by dosing every 12 weeks. 	
Stamp Date	November 28 th , 2007	Route of Administration	Subcutaneous Injection	
Estimated Due Date of OCPB Review	July 29 th , 2008 <i>Mid-Cycle Review: April 28th, 2008.</i>	Sponsor	Centocor Inc., Malvern, PA	
PDUFA Due Date	September 29 th , 2008	Priority Classification	Standard	
Clinical Division Due Date	July 28 th , 2008	BB IND Number	9590	
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Numbers If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			

Reference Bioanalytical and Analytical Methods	X	3		CP2001V-009, CP2007V-001, CP2007V-001
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		C0743T11
multiple dose:				
Patients-				
single dose:	X	2		C0379T01 (IV formulation), C0379T02,
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	2A and 2B		C0379T01 and C0379T02
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			POPPK analysis Report for CNTO 1275 in two Phase 3 Clinical Studies (C743T08 and C)743T09)
In-vivo effects of primary drug:				POPPK Analysis
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X			POPPK ANALYSIS
pediatrics:				
geriatrics:	X			
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		C0379T04
Phase 3 clinical trial:	X	2		C0743T08 and C0743T09
Population Analyses -				
Data rich:				
Data sparse:	X			POPPK analysis Report for CNTO 1275 in two Phase 3 Clinical Studies (C743T08 and C)743T09)
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference (IR):				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Other (in vitro percutaneous absorption study)				
Chronopharmacokinetics				
Pediatric development plan				

Literature References		
Total Number of Studies		9
Fitability and QBR comments		
Types and #'s of studies and supplementary information (literature review) are adequate to conduct a review	"X" if yes X	Comments Filing Meeting on 01/08/08. AC meeting on 06-17-08. Summary of CP for AC due to Clinical Division by 05/14/08
Application filable?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	No	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	Do we need a PM consult? Yes Do we need a Pharmacogenetics consult? Yes	
Other comments or information not included above		
Primary reviewer Signature and Date	Abi Adebowale 01/04/08	
Secondary reviewer Signature and Date	Jang-Ik Lee	

CC: BLA 125261/0, HFD-850 (P.Lee), HFD-540 K.Bhatt), DCP 3 (I. Lee, H. Ahn and D. Bashaw, P.Jadha, J. Gobburu, S. Amur)

Pharmacometrics Review

BLA	STN 125261/0	Submission Date(s)	November 28th, 2007
Brand Name		Pending	
Generic Name		Ustekinumab (ustekinumab)	
Pharmacometrics Reviewer		Pravin Jadhav, Ph.D.	
Pharmacometrics Team Leader		Joga Gobburu, Ph.D.	
Clinical Pharmacology Reviewer		Abimbola Adebawale, Ph.D.	
Clinical Pharmacology Secondary Reviewer		Jang-ik Lee, Pharm.D., Ph.D.	
OCP Division		DCP-3	
OND Division		Division of Dermatologic and ophthalmic drug products (HFD-540)	
Applicant		Centocor Inc., Malvern, PA	
Submission Type; Code		Original BLA	NME
Formulation; Strength(s)		Liquid in vial for subcutaneous injection.	45 mg/ 0.5 mL vial and 90 mg/ 1.0 mL vial
Proposed Indication		Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	
Proposed Dosing Regimen		<p>Patients weighing \leq 100 kg, 45 mg initially and 4 weeks later, followed by dosing every 12 weeks</p> <p>Patients weighing $>$ 100 kg, 90 mg initially and 4 weeks later, followed by dosing every 12 weeks.</p>	

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Executive summary

Ustekinumab (CNTO 1275), a first in class fully human IgG1k mAb to human p40 subunit that binds with high affinity to human IL-12 and IL-23, is being developed to treat adult patients with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Ustekinumab AUC-PASI75 response rate analysis was used to evaluate the sponsor's dosing proposal (45 mg for ≤ 100 Kg subjects and 90 mg for >100 Kg subjects). The key findings of the analysis were-

1. Psoriasis improvement is dependent on serum ustekinumab concentration or AUC.
2. At a given dose, serum concentrations (and AUCs) in heavier subjects are 50% compared to those in lighter subjects.
3. Due to PK differences, the (PASI75) response rate in heavier subject is lower than response rate in lighter subjects.

Based on AUC-PASI response rate analysis, different body weight based dosing adjustments were explored. Each of the dosing strategies explored offer different advantages. Weight based dosing strategy is needed to maximize response rates and the choice should depend on benefit-risk assessment of CNTO 1275.

Recommendations

1. Based on exposure-response analyses, the following 3-step dosing regimen is recommended
 - a. For patients weighing < 70 kg (154 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by dosing every 12 weeks.
 - b. For patients weighing ≥ 70 kg and < 100 kg (220 lbs), the recommended dose is 67.5 mg initially and 4 weeks later, followed by dosing every 12 weeks.
 - c. For patients weighing ≥ 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by dosing every 12 weeks.
2. The claims based on population PK analysis are reasonable.

Pharmacometrics Reviewer:

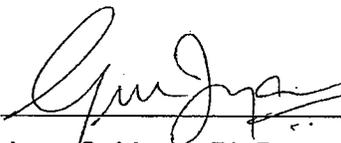
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Introduction

Ustekinumab (CNTO 1275), a first in class fully human IgG1k mAb to human p40 subunit that binds with high affinity to human IL-12 and IL-23, is being developed to treat adult patients with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. It is hypothesized to work by neutralizing IL-12 and IL-23 bioactivity by preventing these cytokines from binding to their IL-12R β 1 (IL-12 receptor beta-1) receptor protein expressed on the surface of immune cells.

Psoriasis

Psoriasis is a chronic inflammatory skin condition requiring lifelong treatment to control frequent flares and remissions. Plaque psoriasis is the most common (~80% of people who develop psoriasis) type of psoriasis characterized by patches of raised, reddish skin covered by silvery-white scale. These patches, or plaques, frequently form on the elbows, knees, lower back, and scalp. Other types of psoriasis are guttate psoriasis (small, red spots on the skin), pustular psoriasis (white pustules surrounded by red skin), inverse psoriasis (smooth, red lesions form in skin folds), and erythrodermic psoriasis (widespread redness, severe itching, and pain).

Statistics: A public health issue[†]

Psoriasis affects an estimated 2-3 percent of the world's population. Approximately, 125 million people worldwide and between 5.8 and 7.5 million Americans have been estimated to have psoriasis. Between 10% and 30% of people who develop psoriasis get a related form of arthritis called "psoriatic arthritis," which causes inflammation of the joints.[‡] Nearly 60 percent psoriasis patients reported their disease to be a large problem in their everyday life. Psoriasis had a greater impact on quality of life in women and younger patients.

Severity measures

Body surface area (BSA) and Psoriasis Area and Severity Index (PASI) score, which combines the extent of psoriasis with local skin signs (erythema, scale and elevation), have been the most frequently used to assess psoriasis severity. Physician's global assessment (PGA) of psoriasis severity has been used as a global static assessment of all lesions on 6- or 7-point scale (from severe to none); it gives a general impression of severity or improvement of psoriasis on treatment.

* <http://www.skincarephysicians.com/psoriasisnet/whatis.html>

† <http://www.psoriasis.org/about/stats/>

‡ <http://www.skincarephysicians.com/psoriasisnet/whatis.html>

Treatment options

Psoriasis treatments can be divided into three main types: topical treatments, light therapy and medications.[§]

Topical treatments

Topical corticosteroids, Vitamin D analogues, Anthralin, Topical retinoids, Calcineurin inhibitors, Coal tar, Moisturizers

Light therapy (phototherapy)

Sunlight, UVB phototherapy, Narrowband UVB therapy, Photochemotherapy, or psoralen plus ultraviolet A (PUVA), Excimer laser and Combination light therapy

Oral or systemic medications

Retinoids, Methotrexate, Azathioprine, Cyclosporine, Hydroxyurea, and immunomodulator drugs (biologics)

The biologics are approved for the treatment of moderate to severe cases of psoriasis. They include alefacept (Amevive), efalizumab (Raptiva), etanercept (Enbrel) and infliximab (Remicade). These drugs are given by intravenous infusion, intramuscular injection or subcutaneous injection and are usually used for people who have failed to respond to traditional therapy or for people with associated psoriatic arthritis.

Major questions

Pharmacometrics review is focused on five major questions:

1. Does exposure response analysis support evidence of effectiveness?
2. Are there any exposure related safety concerns?
3. Based on exposure response analysis, is the sponsor's dosing proposal acceptable?
4. What are the characteristics of the partial and non-responders?
 - a. Does adjusting exposures by switching to q8w regimen help?
5. Are the labeling claims based on population pharmacokinetic model acceptable?

Data

Table 1 summarizes the study population, development phase, dose, route of administration, and sampling scheme of the clinical studies with ustekinumab.

[§] <http://www.mayoclinic.com/health/psoriasis/DS00193/DSECTION=treatments-and-drugs>

Table 1: Listing of ustekinumab clinical studies

Study population	Study number	Study phase	Dose group(s)	Route of administration ^b	Number of subjects evaluated for PK ^d	Sampling scheme ^c
Psoriasis	C0379T01	1	0.09 mg/kg single dose	IV	4	Intensive
			0.27 mg/kg single dose	IV	4	
			0.9 mg/kg single dose	IV	5	
			4.5 mg/kg single dose	IV	5	
	C0379T02	1	0.27 mg/kg single dose	SC	5	Intensive
			0.675 mg/kg single dose	SC	4	
			1.35 mg/kg single dose	SC	4	
			2.7 mg/kg single dose	SC	4	
	C0379T04	2	45 mg single dose	SC	23	Intensive
			90 mg single dose	SC	27	
			45 mg multiple dose	SC	23	
			90 mg multiple dose	SC	21	
C0743T08 (PHOENIX 1)	3	45 mg multiple dose	SC	378 ^e	Sparse	
		90 mg multiple dose	SC	375 ^e		
C0743T09 (PHOENIX 2)	3	45 mg multiple dose	SC	606 ^e	Sparse	
		90 mg multiple dose	SC	606 ^e		
Multiple sclerosis	C0379T03	1	0.27 mg/kg single dose	SC	4	Intensive
			0.675 mg/kg single dose	SC	4	
			1.35 mg/kg single dose	SC	4	
			2.7 mg/kg single dose	SC	4	
	C0743T06	2	27 mg multiple dose	SC	30	Sparse
			90 mg multiple dose	SC	61	
			180 mg multiple dose	SC	30	
Crohn's disease	C0379T07	2	4.5 mg/kg single dose	IV	59	Intensive
			90 mg multiple dose	SC	61	
Healthy Subjects	C0743T11	1	90 mg single dose	SC	31	Intensive

^aIntensive sampling schemes enable determination of the full PK profile using a non-model-based approach (eg, non-compartmental analysis). Sparse sampling schemes require a model-based approach to characterize the full PK profile.
^bSC = subcutaneous, IV = intravenous
^cSubjects randomized to placebo who crossed-over to CNTO 1275 were included.
^dFor C0379T07, C0743T08 and C0743T09, this includes all subjects who received at least 1 administration of CNTO 1275. For C0379T06 the highest sample numbers throughout the sampling timepoints was used.

Source: Sponsor's table 1 from the report summary-clin-pharm.pdf (Page 12 of 80)

Data from a total of 4 studies (C0379T02, C0379T04, PHOENIX I and PHOENIX II) conducted in psoriasis subjects were used in this review.

C0379T02

This was a Phase I, multicenter, randomized, double-blind, placebo-controlled study with single SC administrations of ustekinumab. Twenty-one subjects were randomized to active or placebo treatment within 1 of 4 sequential escalating dose cohorts (0.27 mg/kg, 0.675 mg/kg, 1.35 mg/kg, or 2.7 mg/kg) across 3 sites. The Safety Monitoring Committee completed a blinded comprehensive safety assessment on the 0.27 mg/kg and 0.675 mg/kg dose cohorts before dosing was initiated in the 1.35 mg/kg and 2.7

mg/kg dose cohorts. Each subject received a single dose of ustekinumab or placebo by SC injection. Subjects remained in the clinic for at least 8 hours after administration of study agent and returned for periodic follow-up visits throughout the 24-week study period.

Blood samples for measurement of serum ustekinumab concentration were obtained prior to administration of study agent and at 8, 24, 48, and 72 hours after administration of study agent. In addition, blood samples for the measurement of ustekinumab in the serum were obtained on day 4 and at weeks 1, 2, 4, 8, 12, 16, 20, and 24.

Serum ustekinumab concentrations were measured using a validated enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantification (LLOQ) of 0.09 µg/mL following a 1:10 dilution. Concentrations below the LLOQ were recorded as < 0.09 µg/mL. The baseline concentrations that were labeled as < 0.09 µg/mL were treated as zero. The remaining < 0.09 µg/mL concentrations were excluded from the PK analysis.

C0379T04

This was a multicenter, randomized, double-blind, placebo-controlled study of 2 fixed doses of SC ustekinumab. Subjects were randomized at baseline to 1 of 5 groups: 1) placebo at Weeks 0, 1, 2, and 3; 2) 45 mg single dose ustekinumab at Week 0 and placebo at Weeks 1, 2, and 3; 3) 90 mg single dose ustekinumab at Week 0 and placebo at Weeks 1, 2, and 3; 4) 45 mg weekly × 4 ustekinumab at Weeks 0, 1, 2, and 3; or 5) 90 mg weekly × 4 ustekinumab at Weeks 0, 1, 2, and 3. At Week 16, subjects in the ustekinumab groups who scored ≥ 3 on PGA of psoriasis were to be retreated with 1 additional dose of ustekinumab at the original level (45 or 90 mg); while those with PGA < 3 were to receive placebo. At Week 20, subjects in the placebo group received 90 mg ustekinumab (placebo to 90 mg); subjects in the ustekinumab groups received placebo.

The pharmacokinetics of ustekinumab were determined by assessment of serum ustekinumab concentrations through Week 36. Samples were collected from a subset of subjects at multiple timepoints between Weeks 0 and 36. On days when the study agent was administered, samples were taken immediately before the injection. Serum ustekinumab concentrations were measured using a validated ELISA with a LLOQ of 0.08 µg/mL following a 1:10 dilution.

PHOENIX I (PHOENIX 1) and PHOENIX II (PHOENIX 2)

PHOENIX 1 and PHOENIX 2 were placebo-controlled for the first 12 weeks and identical in design through Week 28. After Week 12, all subjects in PHOENIX 1 and PHOENIX 2 were eligible to receive ustekinumab treatment for approximately 5 years. The 2 studies are currently ongoing. The 2 pivotal Phase 3 psoriasis studies evaluated the liquid in vial formulation and dosing regimens (45 mg and 90 mg SC at Week 0, 4, and then every 12 weeks) intended for the commercial product.

PHOENIX I

This was a multicenter, randomized, placebo-controlled, double-blind, parallel, 3-arm study of SC injections of 45 mg (Group 1), 90 mg (Group 2), and placebo (Group 3) in subjects with moderate to severe plaque psoriasis. PHOENIX 1 enrolled 766 subjects

and the randomization of subjects to treatment was stratified based on investigational site, weight (≤ 90 kg or > 90 kg), and previous experience with conventional systemic therapies (inadequate response to, intolerance to, or contraindication to < 3 or ≥ 3 conventional systemic therapies including cyclosporine, MTX, acitretin, and PUVA).

PHOENIX II

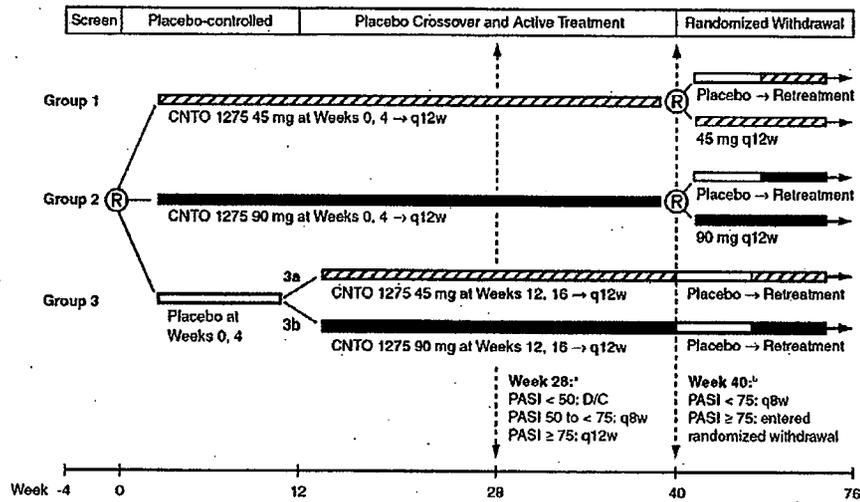
This was a multicenter, randomized, placebo-controlled, double-blind, parallel, 3-arm study of SC injections of ustekinumab 45 mg (Group 1), ustekinumab 90 mg (Group 2), and placebo (Group 3) in subjects with moderate to severe plaque psoriasis. PHOENIX 2 enrolled 1230 subjects and the randomization of subjects to treatment was stratified based on investigational site, weight (≤ 90 kg or > 90 kg), and previous experience with conventional systemic therapies (inadequate response to, intolerance to, or contraindication to < 3 or ≥ 3 conventional systemic therapies including cyclosporine, MTX, acitretin, and PUVA).

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 score ≥ 12 , were to have psoriasis covering $\geq 10\%$ total body surface area, and were to be candidates for phototherapy or systemic therapy. At the beginning of the studies, subjects were randomized 1:1:1 to 45 mg, 90 mg, or placebo. The primary efficacy assessment timepoint was Week 12. At Week 12, subjects randomized to placebo were crossed over to active treatment and at key timepoints subjects were assigned or randomized to various maintenance dosing intervals depending on the subject's response status.

Blood samples for measuring serum ustekinumab concentrations for PK evaluation (in PHOENIX I and II) were collected in all subjects at selected timepoints (Weeks 0, 4, 12, 16, 24, 28, 40, 44, 48 and 52). At visits when study agent was administered, the blood sample for measuring serum ustekinumab concentration was to be taken prior to administration. The actual date and clock time of the more recent dose and PK blood draw at each visit were recorded. Serum ustekinumab concentrations were measured using a validated electrochemiluminescent immunoassay (ECLIA), which was capable of quantifying a serum ustekinumab concentration with a LLOQ of 0.17 $\mu\text{g/mL}$.

Figure 1: Flowchart of studies PHOENIX I (PHOENIX I) and PHOENIX II (PHOENIX II)

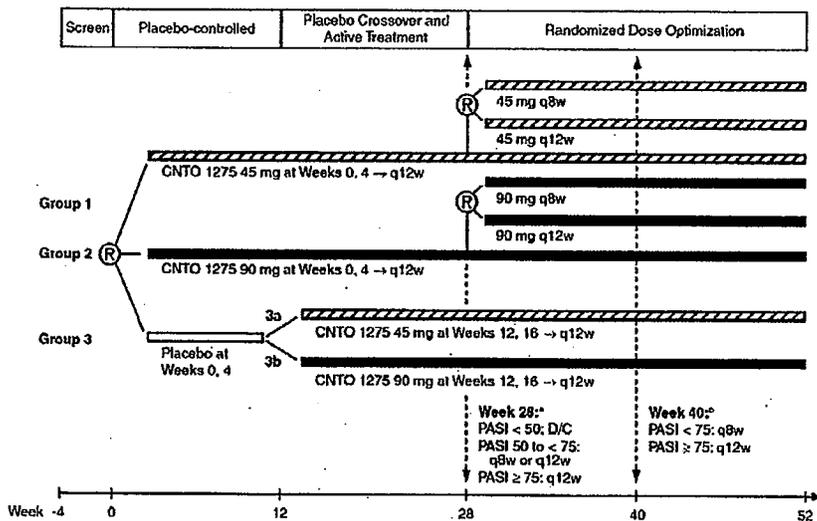
Flow Chart of Study PHOENIX I (PHOENIX I)



D/C = discontinued; PASI = Psoriasis Area and Severity Index; R = randomization; q8w = every 8 weeks; q12w = every 12 weeks
 * At Week 28, in all groups, nonresponders (PASI < 50) discontinued study agent, partial responders (PASI 50 to < 75) began q8w dosing, and PASI responders (PASI ≥ 75) received q12w dosing.
 * At Week 40, PASI responders to q12w dosing in Groups 1 and 2 were randomized to either placebo or continued q12w CNTO 1275 (at their original dose), while those in Group 3 received placebo. At loss of therapeutic effect, subjects receiving placebo began retreatment at their dosing regimen prior to withdrawal. In all groups, nonresponders or partial responders (PASI < 75) were adjusted to q8w dosing. Subjects receiving q8w dosing continued q8w dosing.

11-7113 v6

Flow Chart of Study PHOENIX II (PHOENIX II)



D/C = discontinued; PASI = Psoriasis Area and Severity Index; R = randomization; q8w = every 8 weeks; q12w = every 12 weeks
 * At Week 28, in all groups, nonresponders (PASI < 50) discontinued study agent. In Groups 1 and 2, partial responders (PASI 50 to < 75) were randomized to q8w or q12w dosing and PASI responders (PASI ≥ 75) continued q12w dosing. In Group 3 only, partial responders began q8w dosing and PASI responders began q12w dosing.
 * At Week 40, in all groups, Week 28 PASI responders (PASI ≥ 75) who became nonresponders or partial responders (PASI < 75) were adjusted to q8w dosing and PASI responders continued q12w dosing. Subjects receiving q8w dosing continued q8w dosing.

11-7114 v6

Source: Sponsor's figures 3.2.1 and 3.2.2 from the report pop-pk.pdf (Pages 24 and 26 of 456)

Pivotal trial design features

The two studies had identical design through Week 28. Subjects were randomized to four treatment groups:

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

For subjects originally randomized to active treatment, the treatment regimen consisted on an initial treatment cycle (Weeks 0 and 4) followed by one maintenance dose 12 weeks later. For subjects originally randomized to placebo, following the 12-week placebo controlled period, the subjects received the two initial doses of active treatment. The sponsor submitted data from PHOENIX I through Week 52 and from PHOENIX II through Week 28. In PHOENIX I, the frequency of additional treatments for subjects after Week 16 was based on the Week 28 and Week 40 PASI (Psoriasis Area Severity Index) scores. 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

At Week 40, subjects who were (1) originally randomized to active treatment (groups 1 and 2), (2) Responders at Week 28, and (3) Responders at Week 40 were randomized (1:1) to either continue every 12 week dosing (dose at Week 40) or withdraw treatment (placebo at Week 40).

Dataset source

The following datasets submitted by the sponsor were used in this review.

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Reports

The following reports submitted by the sponsor were used in this review.

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Data summary

The following figures and tables summarize number of subjects available for the analysis per treatment group and demographics from PHOENIX I and II.

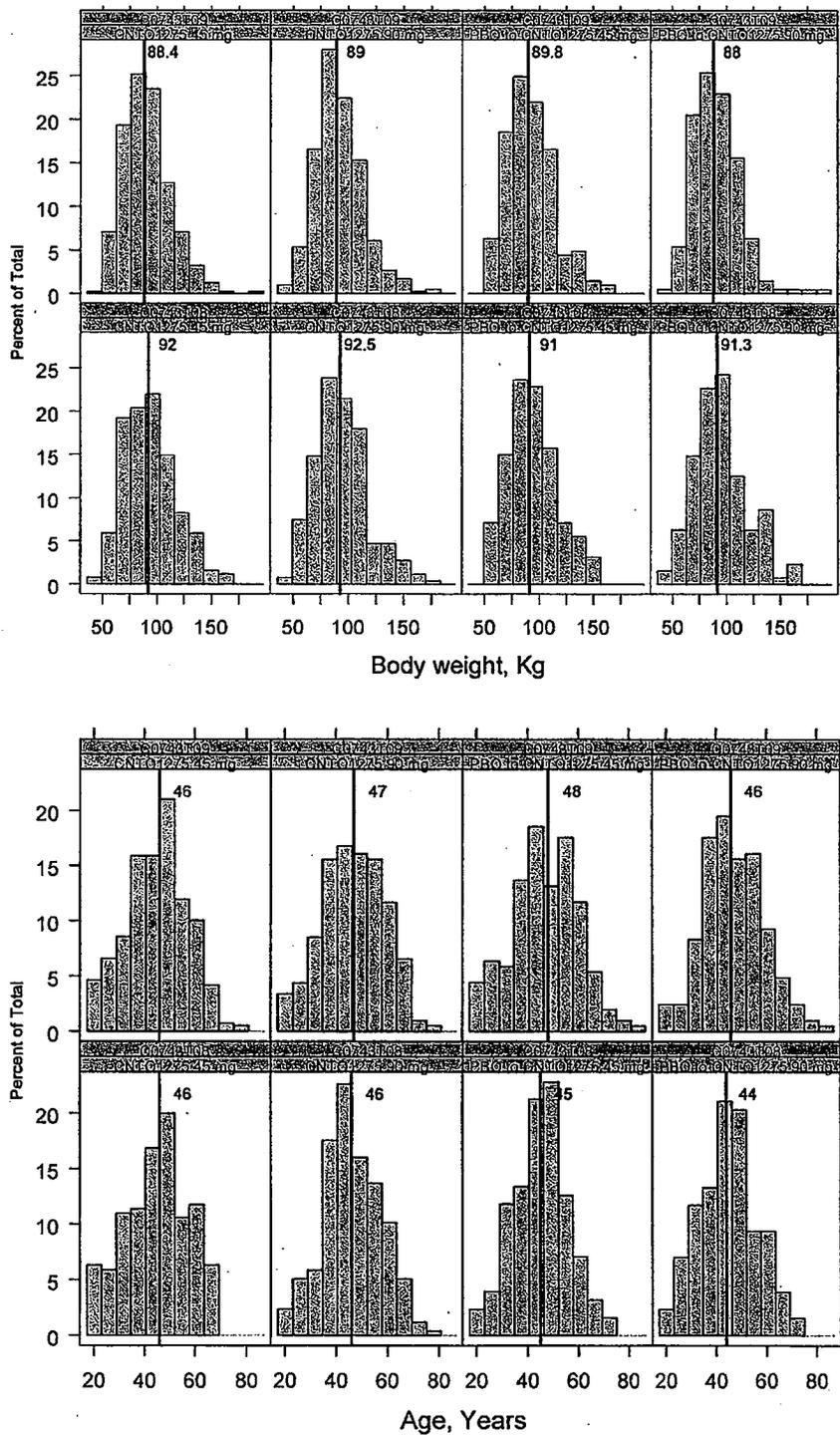
Table 2: Number of subjects per treatment group

	PHOENIX I	PHOENIX II
CNTO 1275 45 mg	255	409
CNTO 1275 90 mg	256	411
PBO to CNTO 1275 45 mg	127	205
PBO to CNTO 1275 90 mg	128	205

Table 3: Distribution of gender and race across treatment groups

Gender		Race				Treatment	Study
Females	Males	Asian	Black	Caucasian	Other		
80	175	2	4	245	4	CNTO 1275 45 mg	PHOENIX I
83	173	6	6	237	7	CNTO 1275 90 mg	PHOENIX I
32	95	5	1	118	3	PBO to CNTO 1275 45 mg	PHOENIX I
40	88	7	3	117	1	PBO to CNTO 1275 90 mg	PHOENIX I
126	283	16	10	372	11	CNTO 1275 45 mg	PHOENIX II
137	274	19	8	375	9	CNTO 1275 90 mg	PHOENIX II
69	136	9	3	191	2	PBO to CNTO 1275 45 mg	PHOENIX II
58	147	6	6	190	3	PBO to CNTO 1275 90 mg	PHOENIX II

Figure 2: Distribution of weight and age across treatment groups



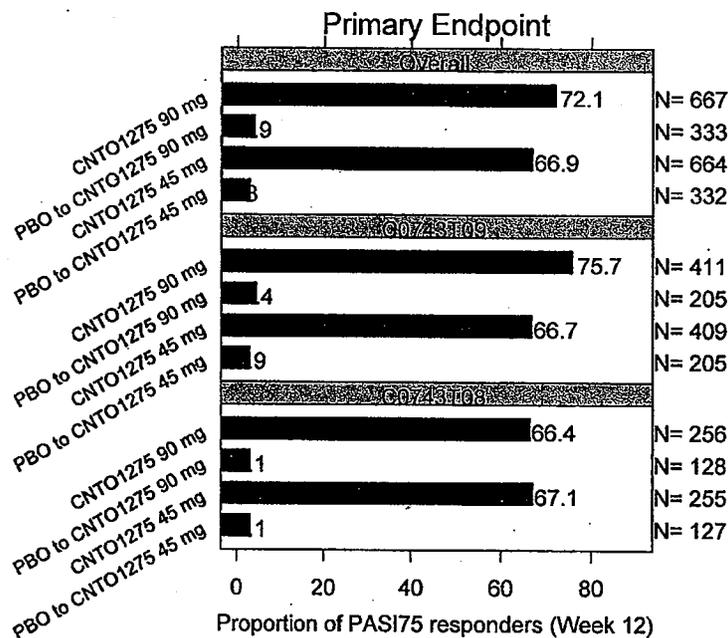
Review questions

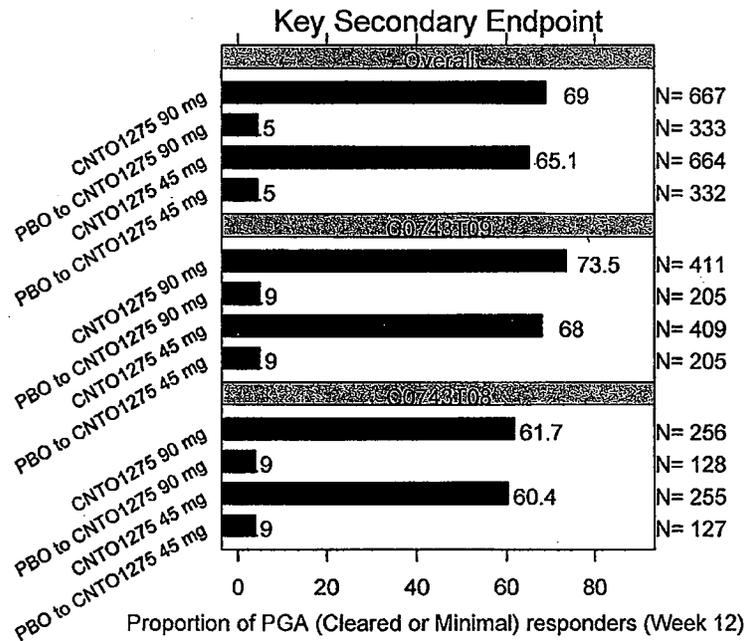
Does exposure response analysis support evidence of effectiveness?

Primary Efficacy and Key Secondary Endpoints (Week 12 analysis)

The primary efficacy endpoint for PHOENIX I and II were PASI75 ($\geq 75\%$ improvement in PASI from baseline to Week 12). The first major secondary endpoint was the proportion of subjects with a Physician's Global Assessment (PGA) of cleared (0) or minimal (1) at Week 12. Both the 45 mg and 90 mg doses of ustekinumab were statistically superior to placebo for PASI75 response and PGA success at Week 12 in both studies. High proportion of PASI75 responders (66.4% to 75.7% across ustekinumab groups in each study) at Week 12 was consistent with results from Phase 2. Comparable high proportion of responders were observed using PGA (60.4% to 73.5% across ustekinumab groups in each study) as a measure of response. The proportion of responders on placebo treated was considerably low (3-5%) in both studies across endpoints. See Figure 3.

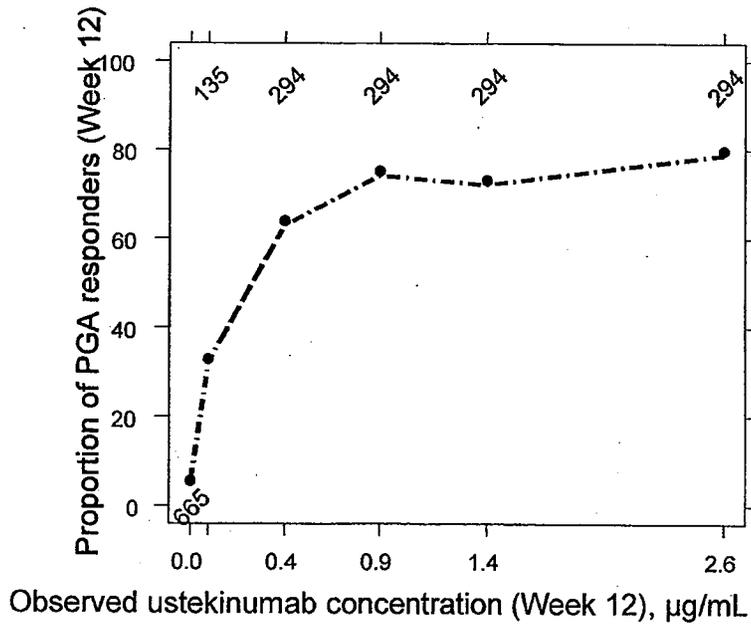
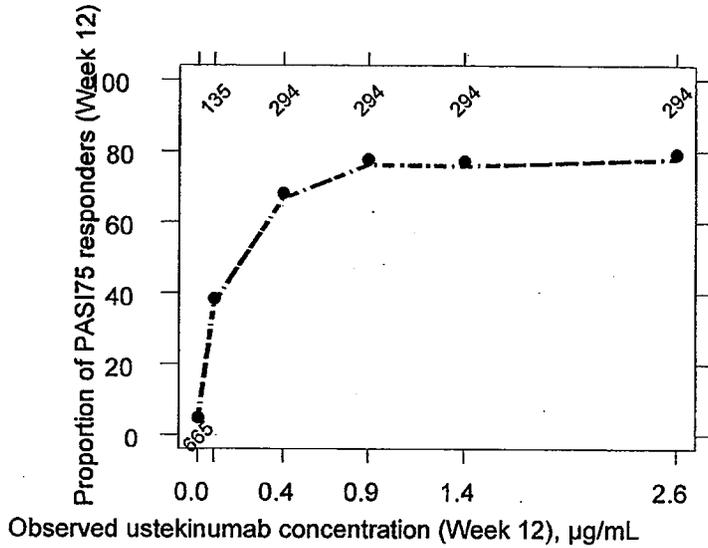
Figure 3: Primary efficacy (PASI75) and major secondary endpoint (PGA) at week 12 by study and overall. The numbers represent response rate and # of subjects in each group.





Serum ustekinumab concentrations were associated with clinical response. Subjects with higher median serum concentrations of ustekinumab generally had greater clinical responses, as measured by PASI or PGA, than subjects with lower median serum concentrations of ustekinumab (Figure 4). For example, the PASI75 response rate at week 12 in 135 subjects that had undetectable serum ustekinumab concentrations was 37% as measured by PASI75. The response rate increased to 75% in subjects with median concentrations $\ge 0.9 \mu\text{g/mL}$.

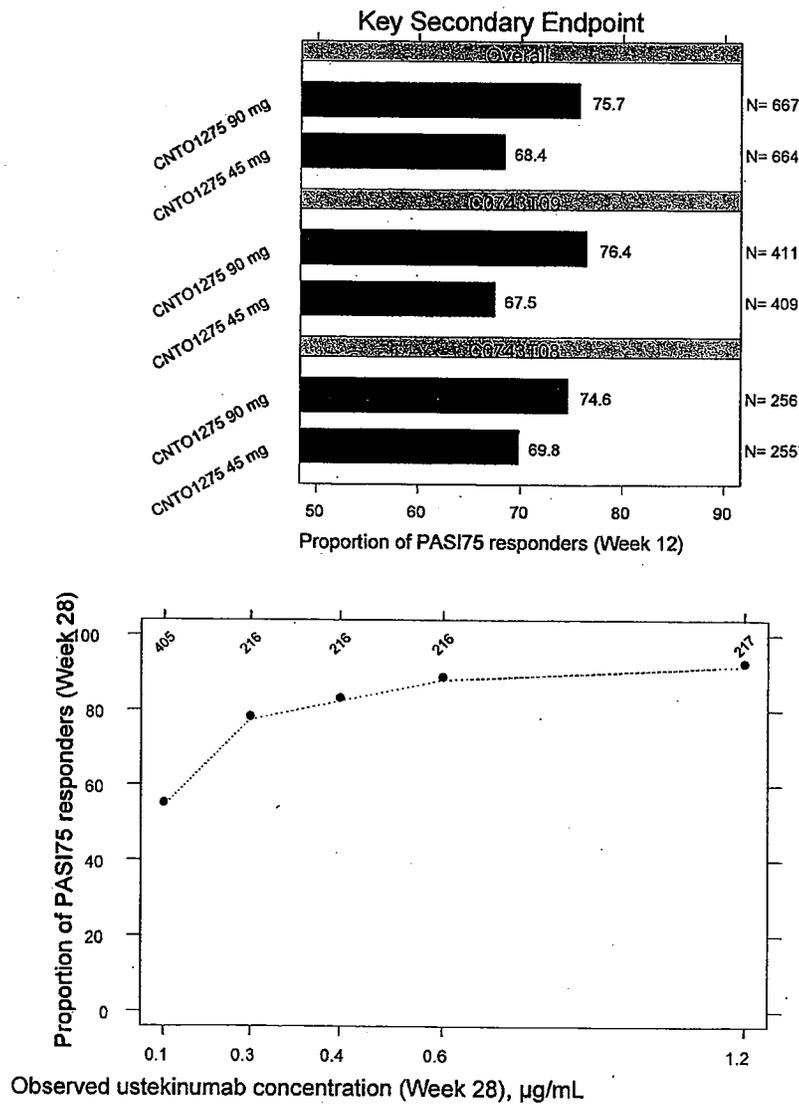
Figure 4: Relationship between serum ustekinumab concentration and proportion of PASI75 responders at week 12 (upper panel) and PGA responders at week 12 (lower panel). Placebo treated subjects and subjects with undetectable ustekinumab concentrations were plotted at ~0.1 $\mu\text{g/mL}$ (0.085 $\mu\text{g/mL}$;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



Key Secondary Endpoint (Week 28 analysis)

These analyses were conducted on week 28 data after subjects received 3 doses of ustekinumab at weeks 0, 4, 16. The proportion of PASI75 responders was slightly higher (68% and 75% overall for 45 and 90 mg, respectively) than at week 12 (67% and 72% overall for 45 and 90 mg, respectively). The exposure response relationship was fairly consistent (Figure 5).

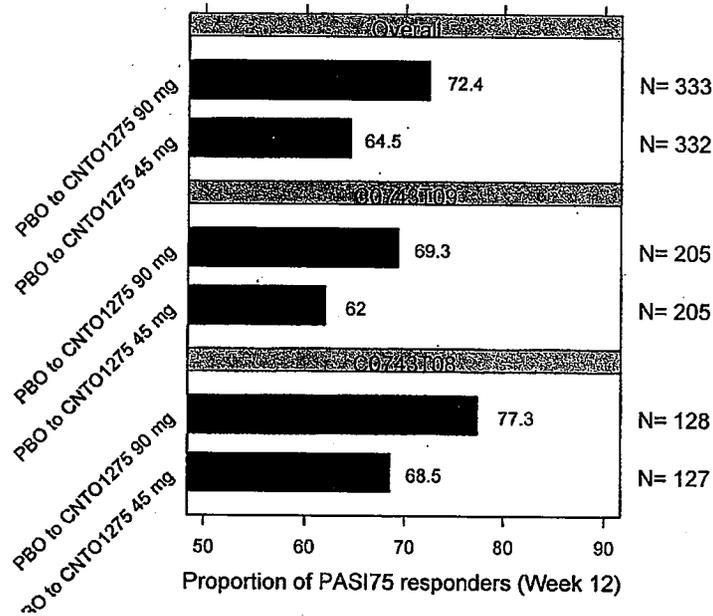
Figure 5: PASI75 analyses at week 28 (similar to week 12 analyses presented above): Comparison of dose groups (upper panel) and exposure-response analysis (lower panel). The numbers represent response rate and # of subjects in each group/quantile.



Placebo crossover group (Week 24 analysis)

These analyses were conducted on week 24 data after subjects who crossed over to ustekinumab at week 12 and received 2 doses of ustekinumab at weeks 12, 16. The expectation was the week 24 data (i.e. 12 weeks of treatment) for placebo crossover group should be similar to week 12 data for subjects randomized to ustekinumab at week 0. Figure 6 and Figure 7 illustrate results at week 24 for placebo crossover group and consistent response across ustekinumab treated groups using combined data (week 12 and 24).

Figure 6: PASI75 analyses at week 24 (similar to week 12 analyses presented above): Comparison of dose groups (upper panel) and combined data from week 12 and week 24 (lower panel). The numbers represent response rate and # of subjects in each group.



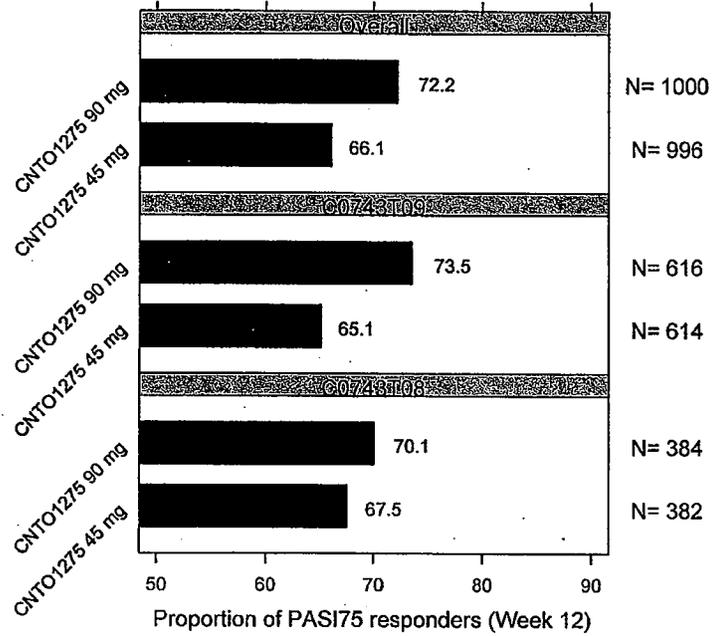
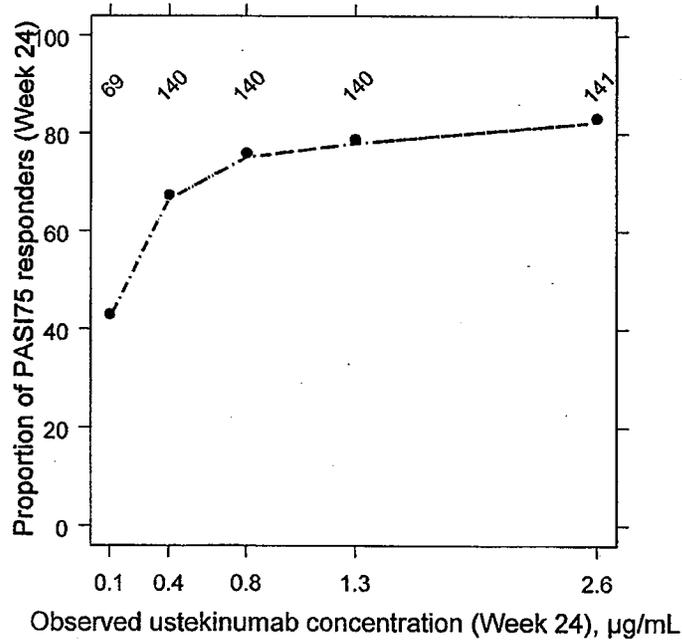
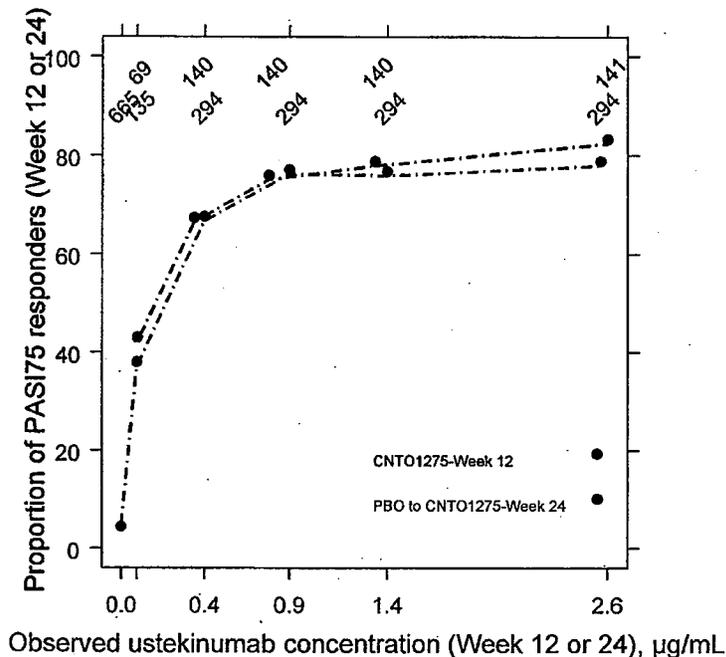


Figure 7: Exposure response analysis at week 24 (similar to week 12 analyses presented above): Comparison of dose groups (upper panel) and combined data from week 12 and week 24 (lower panel). The numbers represent # of subjects in each quantile.





Overall, data were internally consistent (Week 12, 24 and 28 analyses) to support evidence of effectiveness. Serum ustekinumab concentrations were associated with clinical response. Subjects with higher median serum concentrations of ustekinumab generally had greater clinical responses than subjects with lower median serum concentrations of ustekinumab.

Are there any exposure related safety concerns?

For complete safety review, please refer to Dr. Brenda Carr’s medical review.

The major (biologically potential) safety concern for ustekinumab was carcinogenicity due to its mechanism of action by blocking IL-12 and IL-23 expression. No apparent pattern to type of malignancies was observed through 18 months of follow up (source: Dr. Carr’s advisory committee presentation). The sponsor provided safety data for 2,266 subjects with psoriasis who were treated with ustekinumab. The durations of exposures to the product are reported as follows:

- 1,970 subjects treated for ≥ 6 months (994 with 45 mg; 976 with 90 mg)
- 1,285 subjects treated for ≥ 1 year (645 with 45 mg; 640 with 90 mg)
- 373 subjects treated for ≥ 18 months (187 with 45 mg; 186 with 90 mg)

Additionally, there was no obvious dose dependent pattern in overall adverse events (AE), serious AEs, discontinuations due to AE or death (see Table 4).

Table 4: Integrated safety data at week 12.

	Placebo (n=732)	Ustekinumab 45 mg (n=790)	Ustekinumab 90 mg (n=792)
AEs, %	50.4	57.6	51.6
Discontinuation due to AE, %	1.9	1.1	1.4
SAE, %	1.4	1.6	1.4
Death, %	0.0	0.0	0.1

Source: Sponsor's advisory committee slides

Due to the lack of obvious signals, exposure-safety analysis was not conducted.

Based on exposure response analysis, is the sponsor's dosing proposal acceptable?

The proposed dosing recommendations for ustekinumab by the sponsor were:

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

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

Body weight-proportion of PASI75 responders relationship

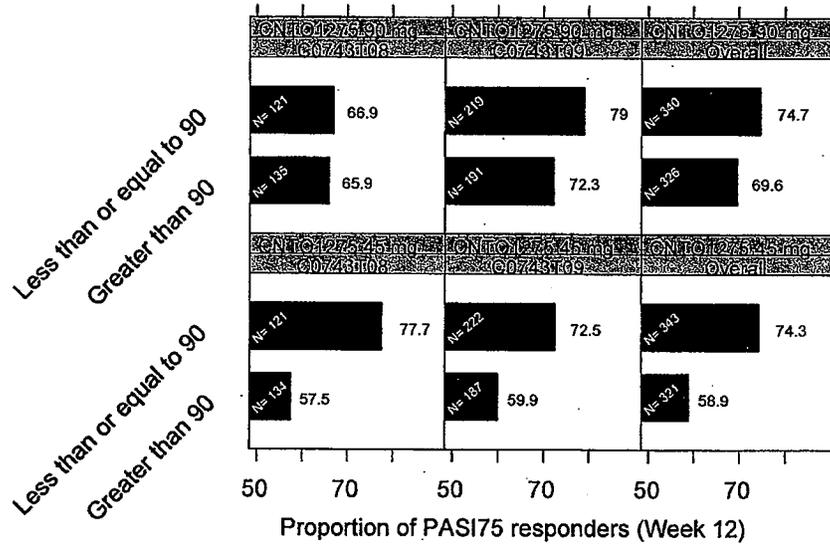
According to the sponsor, the dosing recommendations for ustekinumab were intended to optimize therapeutic efficacy while minimizing unnecessary drug exposure. The 90 mg dosing regimen of ustekinumab showed greater efficacy than the 45 mg dosing regimen. However, the disparity in efficacy resulted primarily from efficacy differences in subjects weighing more than 100 kg, in whom the 90 mg regimen provided efficacy levels approximately 15 to 20 percentage points higher than the 45 mg regimen. This magnitude of efficacy difference, combined with a lack of any apparent impact of dose on safety, was considered clinically meaningful to warrant a recommendation for treatment with the 90 mg dose in subjects > 100 kg in weight. (source: Sponsor's advisory committee background document Page 117 of 139)

These observations are illustrated in a series of plots below (Figure 8 - Figure 10). At a given dose, the proportion PASI75 responders was lower in heavier subjects (body weight greater than or equal to median (90 Kg)). The observation at week 12 (45 mg: 59% vs 74% and 90 mg: 70% vs 75%) was consistent at week 28 (45 mg: 60% vs 76% and 90 mg: 74% vs 77%) in subjects randomized to ustekinumab at week 0 and week 24 (45 mg: 58% vs 74% and 90 mg: 70% vs 75%) in placebo crossover subjects. From the sponsor's analysis of body weight increments (10 Kg), the natural inflection at body

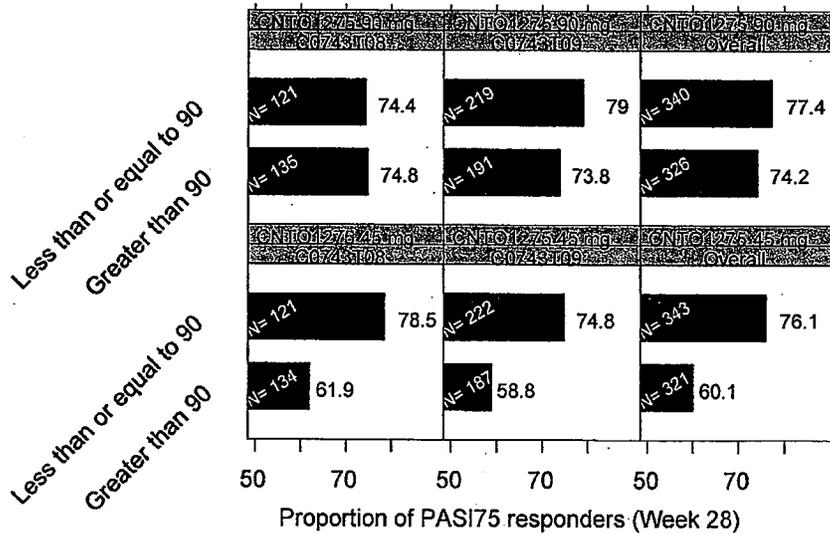
weight=100 Kg formed the basis of the sponsor's proposal to recommend 45 mg to \leq 100 Kg and 90 mg to $>$ 100 Kg subjects. From the reviewer's analysis, PASI response rate (probability) seemed to follow a continuum with respect to body weight as opposed to discrete relationship viewed according to certain body weight cut-off (for example; response rate in subjects $<$ 100kg and \geq 100 kg etc.).

Figure 8: Proportion of PASI75 responders by median body weight (90 kg); at Week 12 and 28 in subjects randomized at Week 0 (Panels A and B); at week 24 in placebo crossover subjects (Panel C) and combined week 12 and 24 data in subjects randomized at Week 0 and placebo crossover (Panel D). The numbers represent response rate and # of subjects in each group.

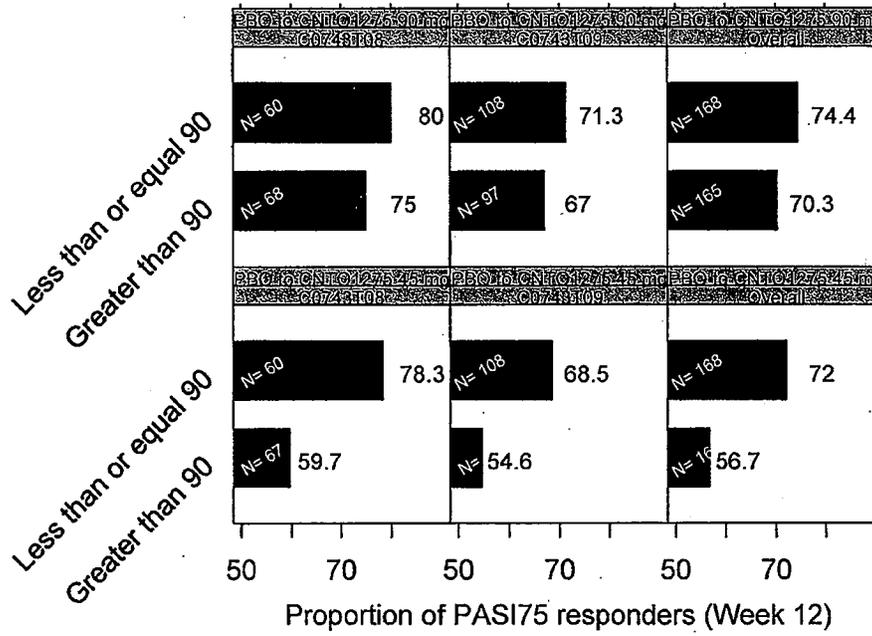
Panel A



Panel B



Panel C



Panel D

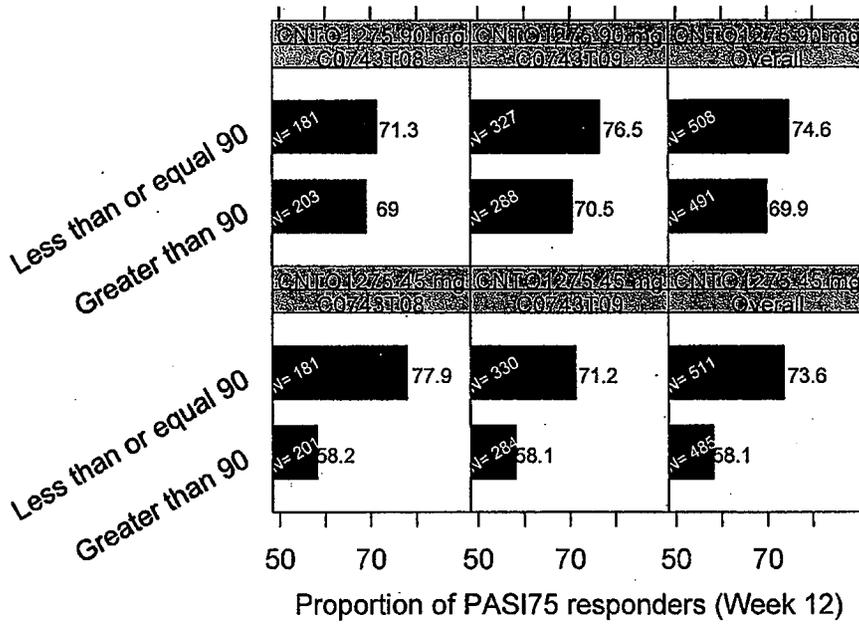
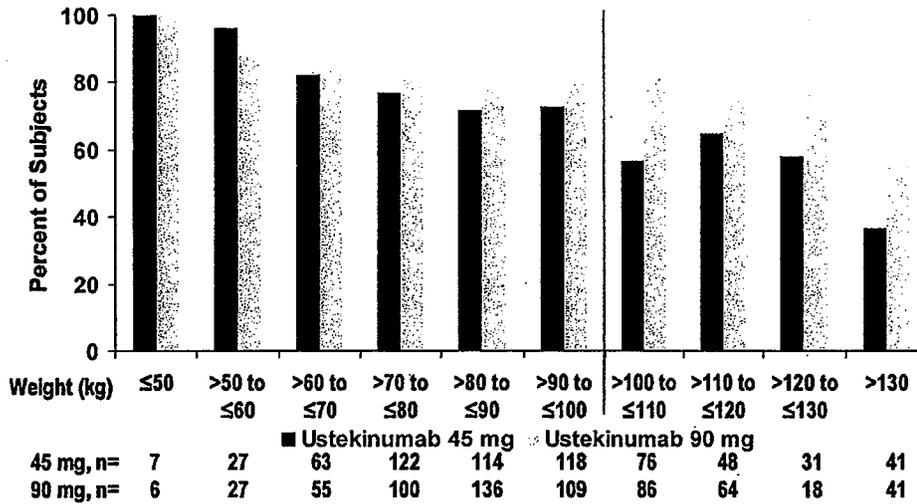
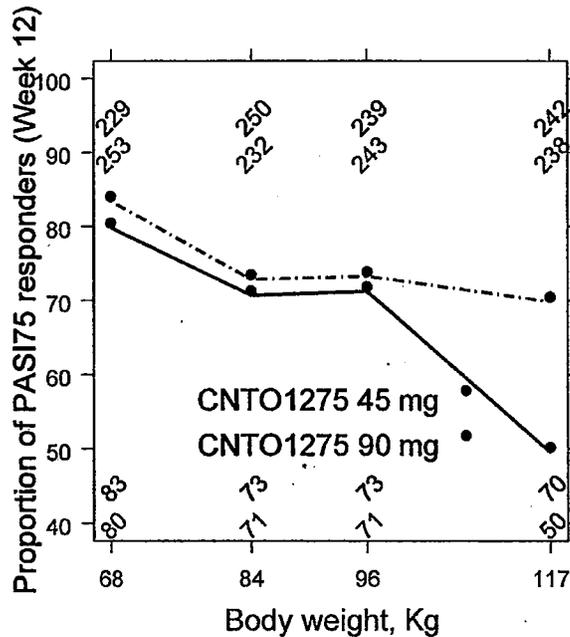


Figure 9: Proportion of PASI75 responders at Week 12 by body weight (10 kg) increments in subjects randomized at Week 0. The numbers at the bottom represent # of subjects at each increment.



(source: Sponsor's advisory committee Slides)

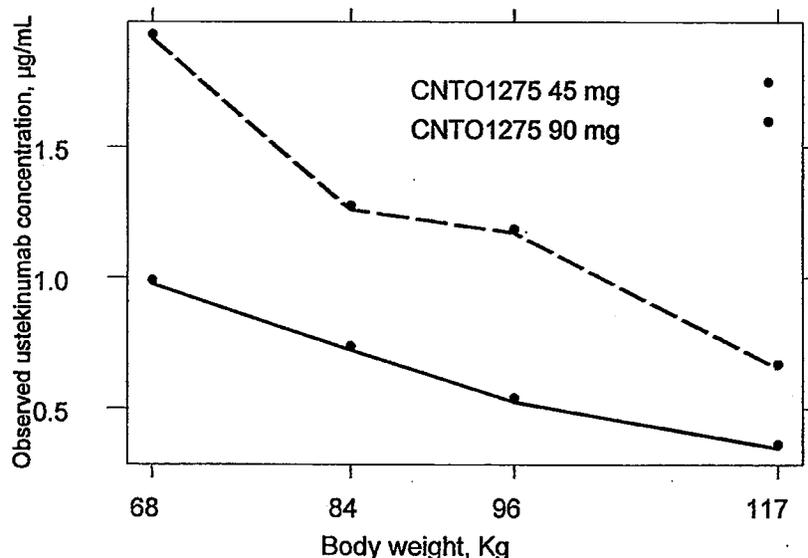
Figure 10: Proportion of PASI75 responders at Week 12 by body weight quantiles from combined week 12 and 24 data in subjects randomized at Week 0 and placebo crossover. The numbers represent response rate (bottom) and # of subjects (top) at each quantile.



Body weight-ustekinumab concentration relationship

Given the relationships between exposure-proportion of PASI75 responders and body weight-proportion of PASI75 responders, the contribution of relationship between weight and ustekinumab pharmacokinetics was investigated. There was a consistent impact of weight on pharmacokinetics and thereby PASI75 response rate. At a given dose, the concentrations in lower body weight group (median weight 68 kg) were two times higher than concentrations in higher body weight group (median weight 117 kg) (Figure 11). As shown earlier, the response rate in the 45 mg group was impacted more (80% vs. 50%) between the highest and lowest weight quantiles. There was a minimal impact of weight on PASI75 response rate in the 90 mg group at both Weeks 12 and 28, because reasonable ustekinumab levels were achieved. For further details on dependency of ustekinumab pharmacokinetics on body weight see the population pharmacokinetic model developed by the sponsor and further extended by the reviewer (See Appendix II: Population Pharmacokinetics analysis).

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



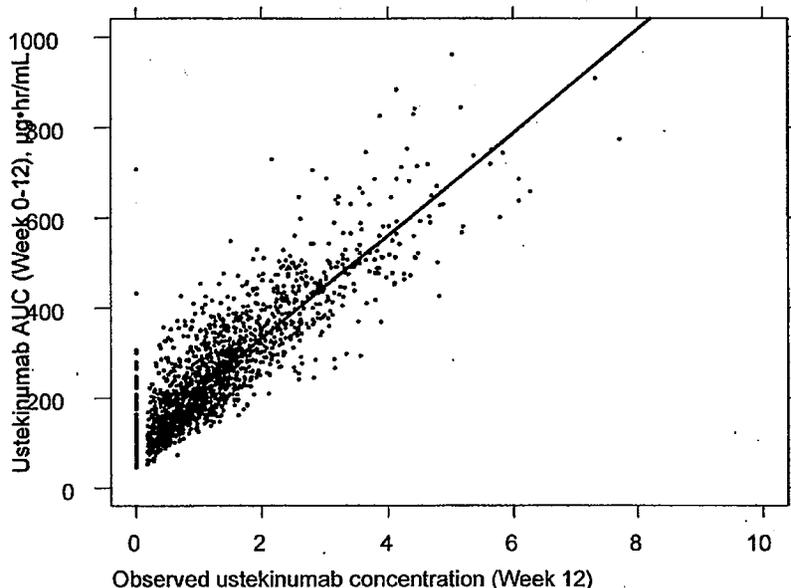
Therefore, the PK and PASI75 response rate (probability) follow a continuum with respect to body weight as opposed to discrete relationship viewed according to body weight cut-off (for example; response rate in subjects <100kg and ≥100 kg etc.).

Evaluation of alternate dosing regimens

Given the dependency of ustekinumab exposures on body weight, and PASI75 response rates on ustekinumab exposure, one dose is not be optimum. The population pharmacokinetic model developed by the sponsor was used to derive AUCs in individual subjects. Ustekinumab AUC (Week 0-12) – response (proportion of PASI75 responders) model was developed to evaluate alternate dosing regimen. The model

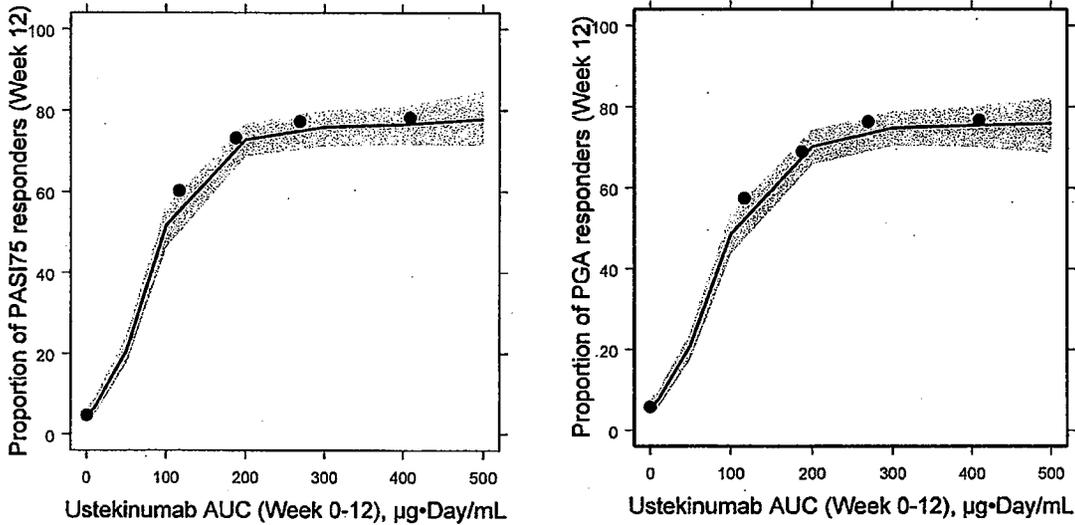
helped us gain insights into dosing regimens in order to maximize PASI75 response rate. Ustekinumab AUC was used instead of observed concentration to account for intersubject variability in pharmacokinetics affecting response rate, especially for subjects with undetectable ustekinumab concentration at week 12. As shown below, concentration and AUC were collinear and thus were used interchangeably.

Figure 12: Collinearity between ustekinumab AUC (Week 0-12) and concentration at week 12.



The AUC-PASI75 and AUC-PGA response rate model developed using logistic regression and generalized additive models (GAM) described the data fairly well as shown in Figure 13. Ustekinumab was the most important predictor of PASI75. See Appendix III: Exposure (ustekinumab AUC)- response (PASI75 and PGA) analysis.

Figure 13: Relationship between ustekinumab AUC (Week 0-12) and proportion of PASI75 and PGA responders. The line represents median prediction and shaded area represents 95% CI of likelihood (PASI75 and PGA) at week 12 as a function of ustekinumab AUC. The dots represent observed quantiles.



The AUC-PASI75 response rate model was used to explore alternate dosing regimens (Table 5), such as one dose for all (45 or 90 mg) and several weight based dosing regimens. The population pharmacokinetic model developed by the sponsor was used to simulate AUCs in individual subjects after new dosing regimen using individual post-hoc estimates. The aim was to derive a regimen that might yield optimal PASI75 response rate for entire population. According to the observed data as well as model predictions, a 45 mg dose is suboptimal in higher body weight subjects and a 90 mg dose does offer higher benefit in these subjects.

Table 5: Predicted response rates under different dosing regimens based on the AUC-proportion of PASI75 responders model

Dosing strategy	Dose	Predicted Response Rate (%) (Overall and by weight cut offs)			
		Overall	<70kg	≥70-<100kg	≥100kg
One dose for all	45	65	80	68	54
One dose for all	90	75	84	76	70
Weight based dosing adjustments					
Two-Step	<100kg: 45mg	70	80	68	70

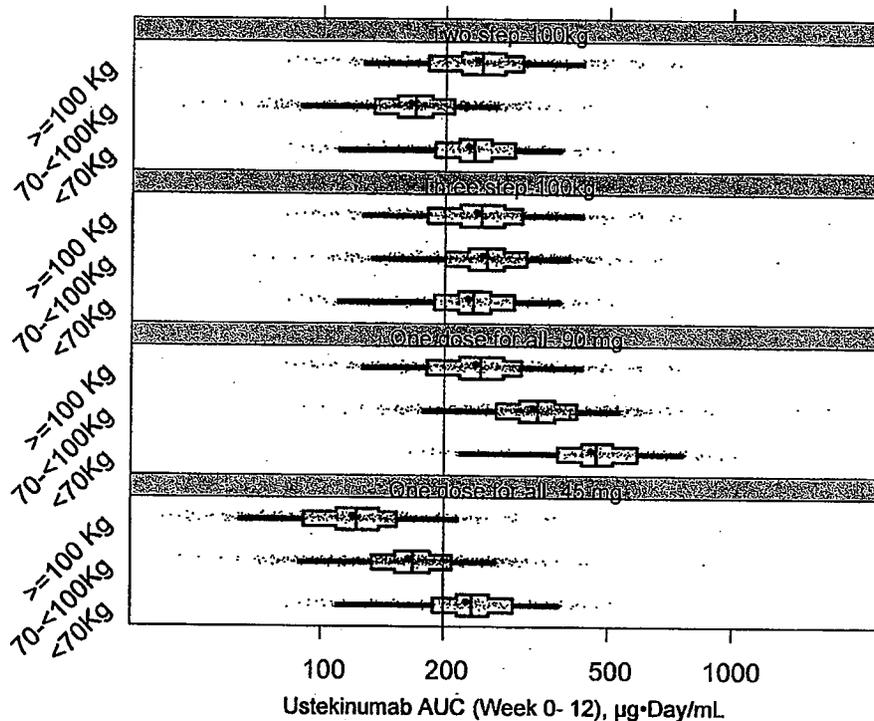
	≥100kg: 90mg				
Three-Step	<70kg: 45mg ≥70-<100kg: (0.75mL) 67.5mg ≥100kg: 90mg	73	80	74	70
Five Step	<45kg: 45mg ≥45-<60kg: 0.6mL(54 mg) ≥60-<75kg: 0.75mL(67.5 mg) ≥75-<90kg: 0.9mL(81 mg) ≥90kg: 90mg	75	82	75	70
Semi-Continuous	<45kg: 45mg 45-90kg: 1mg/kg ≥90kg: 90mg	75	82	75	70

The key findings from exploring alternative dosing regimen were:

- PASI75 response rate can be further maximized by weight based adjustment.
 - Administration of ustekinumab based on two step body weight cut off (100 kg) increases the overall response rate to 70% with the gains in heavier subjects.
 - Administration of ustekinumab based on 3 step body weight cut offs (<70, ≥70-<100 and ≥100 kg) or 5 step body weight cut offs (<45, ≥45-<60, ≥60-<75, ≥75-90 and >90 kg) or semi-continuous (mg/kg) weight based dosing could yield PASI75 response rate comparable to administration of 90 mg to all subjects (overall 75%).
- None of the body weight based adjustments will yield AUCs in excess of those observed after 90 mg administration. All predictions are within the observed AUC ranges (see Figure 14).
- Each of the body weight based adjustments explored here offer precise control over pharmacokinetics in the order listed in Table 5.
- In the same order the necessity of accurate dose calculation seem to increase.
- These data were presented to the advisory committee (<http://www.fda.gov/ohrms/dockets/ac/cder08.html#DermatologicOphthalmicDrugs>) on June 17, 2008, the two step dosing proposal was recommended by 7 votes vs 3 votes for three step dosing proposal.
 - The main concerns from the committee were
 - Lack of empirical data at 67.5 mg
 - Possible delays in generating stability data for 67.5 mg
 - Lack of availability of information on the lowest effective dose
- Finally, each of the dosing strategies explored here offer different advantages. In reviewer's opinion, all the concerns above can be alleviated through objective discussions. Because the perceived benefit needs to be clinically justified, the reviewer found the discussion at advisory committee meeting useful. The open

public hearing added to the gravity of psoriasis in social setting, thus maximizing responder rate should be the goal of these therapies. Based on increased benefit and lack of any exposure related safety concerns, the reviewer recommends three step dosing regimen.

Figure 14: Predicted exposures for different dosing regimen. The scattered dots represent individual subject data.



What are the characteristics of the partial and non-responders?

Body weight and ustekinumab dose (exposure) were two major determinants for partial or non-response at week 12. In subjects weighing >100 kg (PHOENIX I), there were 26.5% partial and 19.5% non-responders in 45 mg group compared 17.4% partial and 14.1% non-responders in 90 mg group. In subjects weighing ≤100 kg, there were 11.3% partial and 14.9% non-responders in 45 mg group compared 20.9% partial and 14% non-responders in 90 mg group. In subjects weighing >100 kg (PHOENIX II), there were 25% partial and 25.9% non-responders in 45 mg group compared 16.5% partial and 12.4% non-responders in 90 mg group. In subjects weighing ≤100 kg, there were 13.8% partial and 12.8% non-responders in 45 mg group compared 12.4% partial and 9.7% non-responders in 90 mg group. A series of tables (Table 6-Table 9) below demonstrate effect dose and body weight as determinant for PASI90, PASI75 and PASI50 response.

Table 6: Proportion of subjects with PASI 50, PASI 75, and PASI 90 responses through Week 12; subjects randomized at Week 0 to CNTO 1275 in psoriasis Phase 3

	<u>PHOENIX 1</u>		<u>PHOENIX 2</u>	
	<u>45 mg</u>	<u>90 mg</u>	<u>45 mg</u>	<u>90 mg</u>
Subjects randomized at Week 0	255	256	409	411
Week 2				
n	255	255	402	411
≥ 90% improvement	0 (0.0%)	1 (0.4%)	1 (0.2%)	2 (0.5%)
≥ 75% improvement	4 (1.6%)	1 (0.4%)	7 (1.7%)	10 (2.4%)
≥ 50% improvement	24 (9.4%)	25 (9.8%)	48 (11.9%)	47 (11.4%)
Week 4				
n	255	253	407	409
≥ 90% improvement	4 (1.6%)	5 (2.0%)	20 (4.9%)	23 (5.6%)
≥ 75% improvement	22 (8.6%)	31 (12.3%)	69 (17.0%)	80 (19.6%)
≥ 50% improvement	109 (42.7%)	103 (40.7%)	179 (44.0%)	214 (52.3%)
Week 8				
n	255	249	405	407
≥ 90% improvement	56 (22.0%)	46 (18.5%)	119 (29.4%)	139 (34.2%)
≥ 75% improvement	133 (52.2%)	125 (50.2%)	227 (56.0%)	260 (63.9%)
≥ 50% improvement	201 (78.8%)	200 (80.3%)	330 (81.5%)	348 (85.5%)
Week 12				
n	255	256	409	411
≥ 90% improvement	106 (41.6%)	94 (36.7%)	173 (42.3%)	209 (50.9%)
≥ 75% improvement	171 (67.1%)	170 (66.4%)	273 (66.7%)	311 (75.7%)
≥ 50% improvement	213 (83.5%)	220 (85.9%)	342 (83.6%)	367 (89.3%)

Table 7: Proportion of subjects with PASI 50, PASI 75, and PASI 90 responses through Week 12; subjects randomized at Week 0 to CNTO 1275 in psoriasis Phase 3

	<u>PHOENIX 1</u>		<u>PHOENIX 2</u>	
	<u>45 mg</u>	<u>90 mg</u>	<u>45 mg</u>	<u>90 mg</u>
Subjects randomized at Week 0	255	256	409	411
Week 12				
n	255	256	409	411
≥ 90% improvement	106 (41.6%)	94 (36.7%)	173 (42.3%)	209 (50.9%)
≥ 75% improvement	171 (67.1%)	170 (66.4%)	273 (66.7%)	311 (75.7%)
≥ 50% improvement	213 (83.5%)	220 (85.9%)	342 (83.6%)	367 (89.3%)
Week 16				
n	254	248	402	403
≥ 90% improvement	115 (45.3%)	120 (48.4%)	173 (43.0%)	206 (51.1%)
≥ 75% improvement	172 (67.7%)	179 (72.2%)	272 (67.7%)	314 (77.9%)
≥ 50% improvement	214 (84.3%)	215 (86.7%)	342 (85.1%)	363 (90.1%)
Week 20				
n	250	248	399	401
≥ 90% improvement	135 (54.0%)	144 (58.1%)	202 (50.6%)	242 (60.3%)
≥ 75% improvement	187 (74.8%)	205 (82.7%)	299 (74.9%)	335 (83.5%)
≥ 50% improvement	226 (90.4%)	233 (94.0%)	358 (89.7%)	376 (93.8%)
Week 24				
n	251	246	397	403
≥ 90% improvement	140 (55.8%)	156 (63.4%)	202 (50.9%)	240 (59.6%)
≥ 75% improvement	191 (76.1%)	209 (85.0%)	292 (73.6%)	335 (83.1%)
≥ 50% improvement	226 (90.0%)	235 (95.5%)	366 (92.2%)	376 (93.3%)
Week 28				
n	250	243	397	400
≥ 90% improvement	123 (49.2%)	135 (55.6%)	178 (44.8%)	217 (54.3%)
≥ 75% improvement	178 (71.2%)	191 (78.6%)	276 (69.5%)	314 (78.5%)
≥ 50% improvement	228 (91.2%)	234 (96.3%)	369 (92.9%)	380 (95.0%)

Table 8: Summary of PASI response through Week 12 by visit; subjects randomized at Week 0 with weight ≤ 100 kg at Week 0

PHOENIX I

	Placebo	CNTO 1275	
		45 mg	90 mg
Subjects randomized at Week 0 with weight ≤ 100 kg at Week 0	166	168	164
Week 2			
n	165	168	163
≥ 90% improvement	0 (0.0%)	0 (0.0%)	1 (0.6%)
≥ 75% improvement	0 (0.0%)	4 (2.4%)	1 (0.6%)
≥ 50% improvement	4 (2.4%)	16 (9.5%)	17 (10.4%)
Week 4			
n	165	168	161
≥ 90% improvement	0 (0.0%)	3 (1.8%)	4 (2.5%)
≥ 75% improvement	1 (0.6%)	18 (10.7%)	22 (13.7%)
≥ 50% improvement	7 (4.2%)	83 (49.4%)	69 (42.9%)
Week 8			
n	163	168	159
≥ 90% improvement	1 (0.6%)	43 (25.6%)	33 (20.8%)
≥ 75% improvement	3 (1.8%)	103 (61.3%)	84 (52.8%)
≥ 50% improvement	12 (7.4%)	136 (81.0%)	129 (81.1%)
Week 12			
n	166	168	164
≥ 90% improvement	4 (2.4%)	79 (47.0%)	66 (40.2%)
≥ 75% improvement	6 (3.6%)	124 (73.8%)	107 (65.2%)
≥ 50% improvement	19 (11.4%)	143 (85.1%)	141 (86.0%)

PHOENIX II

	Placebo	CNTO 1275	
		45 mg	90 mg
Subjects randomized at Week 0 with weight ≤ 100 kg at Week 0	290	297	289
Week 2			
n	288	292	289
≥ 90% improvement	0 (0.0%)	1 (0.3%)	1 (0.3%)
≥ 75% improvement	0 (0.0%)	6 (2.1%)	8 (2.8%)
≥ 50% improvement	6 (2.1%)	44 (15.1%)	35 (12.1%)
Week 4			
n	289	296	287
≥ 90% improvement	0 (0.0%)	18 (6.1%)	19 (6.6%)
≥ 75% improvement	3 (1.0%)	62 (20.9%)	66 (23.0%)
≥ 50% improvement	19 (6.6%)	150 (50.7%)	155 (54.0%)
Week 8			
n	286	295	287
≥ 90% improvement	2 (0.7%)	103 (34.9%)	107 (37.3%)
≥ 75% improvement	9 (3.1%)	183 (62.0%)	190 (66.2%)
≥ 50% improvement	28 (9.8%)	251 (85.1%)	248 (86.4%)
Week 12			
n	290	297	289
≥ 90% improvement	1 (0.3%)	146 (49.2%)	159 (55.0%)
≥ 75% improvement	12 (4.1%)	218 (73.4%)	225 (77.9%)
≥ 50% improvement	33 (11.4%)	259 (87.2%)	261 (90.3%)

Table 9: Summary of PASI response through Week 12 by visit; subjects randomized at Week 0 with weight >100 kg at Week 0

	PHOENIX I		
	Placebo	CNTO 1275	
		45 mg	90 mg
Subjects randomized at Week 0 with weight > 100 kg at Week 0	89	87	92
Week 2			
n	89	87	92
≥ 90% improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥ 75% improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥ 50% improvement	2 (2.2%)	8 (9.2%)	8 (8.7%)
Week 4			
n	89	87	92
≥ 90% improvement	0 (0.0%)	1 (1.1%)	1 (1.1%)
≥ 75% improvement	0 (0.0%)	4 (4.6%)	9 (9.8%)
≥ 50% improvement	3 (3.4%)	26 (29.9%)	34 (37.0%)
Week 8			
n	89	87	90
≥ 90% improvement	1 (1.1%)	13 (14.9%)	13 (14.4%)
≥ 75% improvement	2 (2.2%)	30 (34.5%)	41 (45.6%)
≥ 50% improvement	5 (5.6%)	65 (74.7%)	71 (78.9%)
Week 12			
n	89	87	92
≥ 90% improvement	1 (1.1%)	27 (31.0%)	28 (30.4%)
≥ 75% improvement	2 (2.2%)	47 (54.0%)	63 (68.5%)
≥ 50% improvement	7 (7.9%)	70 (80.5%)	79 (85.9%)

PHOENIX II

	Placebo	CNTO 1275	
		45 mg	90 mg
Subjects randomized at Week 0 with weight > 100 kg at Week 0	120	112	121
Week 2			
n	120	110	121
≥ 90% improvement	0 (0.0%)	0 (0.0%)	1 (0.8%)
≥ 75% improvement	0 (0.0%)	1 (0.9%)	2 (1.7%)
≥ 50% improvement	1 (0.8%)	4 (3.6%)	12 (9.9%)
Week 4			
n	120	111	121
≥ 90% improvement	0 (0.0%)	2 (1.8%)	4 (3.3%)
≥ 75% improvement	0 (0.0%)	7 (6.3%)	14 (11.6%)
≥ 50% improvement	2 (1.7%)	29 (26.1%)	59 (48.8%)
Week 8			
n	120	110	119
≥ 90% improvement	0 (0.0%)	16 (14.5%)	32 (26.9%)
≥ 75% improvement	0 (0.0%)	44 (40.0%)	70 (58.8%)
≥ 50% improvement	4 (3.3%)	79 (71.8%)	100 (84.0%)
Week 12			
n	120	112	121
≥ 90% improvement	2 (1.7%)	27 (24.1%)	50 (41.3%)
≥ 75% improvement	3 (2.5%)	55 (49.1%)	86 (71.1%)
≥ 50% improvement	8 (6.7%)	83 (74.1%)	106 (87.6%)

Does adjusting exposures by switching to q8w regimen offer more benefit in partial responders?

At the time of this review, data from PHOENIX II were not available for review. PHOENIX I examined whether subjects who inadequately responded to q12w dosing would respond to dosing interval adjustment. Subjects who were partial responders at Week 28 underwent dosing interval adjustment to q8w dosing. By Week 40, approximately 40% to 50% of partial responders achieved a PASI 75 response after dosing interval adjustment to q8w, and this proportion of PASI 75 responders was maintained over time through Week 56. Moreover, approximately 15% to 20% of subjects achieved and maintained a PASI 90 (Table 10) response, and approximately 80% maintained at least a PASI 50 response. Similar observations were seen in subjects who were PASI 75 responders at Week 28 but not at Week 40 who then had their dosing interval adjusted to q8w. Regardless whether subjects had been PASI 75

responders at the visit prior to dosing interval adjustment (i.e., at Week 24), substantial proportions of subjects achieved PASI 75 response with dosing interval adjustment to q8wk dosing, though response rates were higher in subjects who had been PASI 75 responders at Week 24. Similar patterns of response were observed in PGA scores.

Overall, q8w seem to offer some benefit in partial responders. Exposure-response analysis was not conducted at this time due to availability data from limited number of subjects. Comparing q12w and q8w regimen with exposure-response analyses will be useful once data from PHOENIX II are available.

Table 10: Summary of PASI response from Week 12 through Week 56 by visit; subjects whose dosing interval was adjusted to q8 weeks at Week 28

	CNTO 1275			
	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg
Subjects whose dosing interval was adjusted to q8 weeks at Week 28	37	16	49	44
Week 12				
n	37	16	49	44
≥ 90% improvement	0 (0.0%)	0 (0.0%)	6 (12.2%)	3 (6.8%)
≥ 75% improvement	0 (0.0%)	0 (0.0%)	14 (28.6%)	11 (25.0%)
≥ 50% improvement	0 (0.0%)	0 (0.0%)	32 (65.3%)	29 (65.9%)
Week 16				
n	37	16	49	44
≥ 90% improvement	0 (0.0%)	0 (0.0%)	2 (4.1%)	4 (9.1%)
≥ 75% improvement	1 (2.7%)	1 (6.3%)	10 (20.4%)	7 (15.9%)
≥ 50% improvement	8 (21.6%)	6 (37.5%)	31 (63.3%)	24 (54.5%)
Week 20				
n	36	16	48	44
≥ 90% improvement	1 (2.8%)	1 (6.3%)	4 (8.3%)	3 (6.8%)
≥ 75% improvement	7 (19.4%)	5 (31.3%)	18 (37.5%)	17 (38.6%)
≥ 50% improvement	24 (66.7%)	14 (87.5%)	40 (83.3%)	37 (84.1%)
Week 24				
n	37	16	49	44
≥ 90% improvement	2 (5.4%)	1 (6.3%)	4 (8.2%)	4 (9.1%)
≥ 75% improvement	10 (27.0%)	4 (25.0%)	19 (38.8%)	19 (43.2%)
≥ 50% improvement	30 (81.1%)	12 (75.0%)	42 (85.7%)	41 (93.2%)
Week 28				
n	37	16	49	44
≥ 90% improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥ 75% improvement	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≥ 50% improvement	37 (100.0%)	16 (100.0%)	49 (100.0%)	43 (97.7%)

CNTO 1275

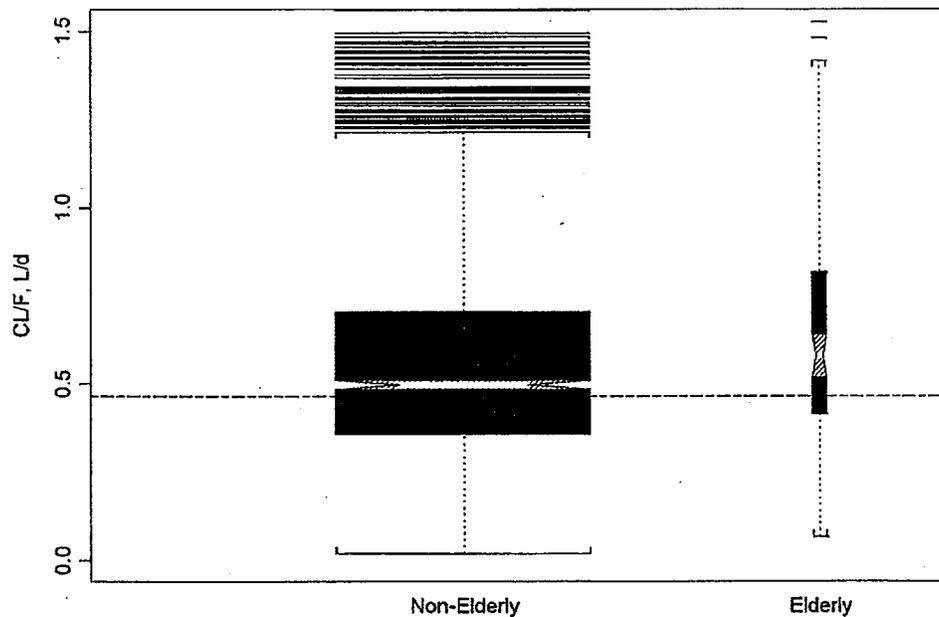
	Placebo → 45 mg	Placebo → 90 mg	45 mg	90 mg
Week 32				
n	36	16	49	44
≥ 90% improvement	3 (8.3%)	2 (12.5%)	0 (0.0%)	1 (2.3%)
≥ 75% improvement	8 (22.2%)	5 (31.3%)	22 (44.9%)	12 (27.3%)
≥ 50% improvement	31 (86.1%)	16 (100.0%)	46 (93.9%)	42 (95.5%)
Week 36				
n	37	16	49	43
≥ 90% improvement	3 (8.1%)	2 (12.5%)	2 (4.1%)	3 (7.0%)
≥ 75% improvement	13 (35.1%)	4 (25.0%)	22 (44.9%)	14 (32.6%)
≥ 50% improvement	29 (78.4%)	15 (93.8%)	42 (85.7%)	40 (93.0%)
Week 40				
n	37	16	49	44
≥ 90% improvement	4 (10.8%)	3 (18.8%)	9 (18.4%)	4 (9.1%)
≥ 75% improvement	15 (40.5%)	6 (37.5%)	22 (44.9%)	16 (36.4%)
≥ 50% improvement	31 (83.8%)	13 (81.3%)	43 (87.8%)	42 (95.5%)
Week 44				
n	37	16	49	43
≥ 90% improvement	3 (8.1%)	3 (18.8%)	7 (14.3%)	5 (11.6%)
≥ 75% improvement	16 (43.2%)	5 (31.3%)	25 (51.0%)	18 (41.9%)
≥ 50% improvement	31 (83.8%)	11 (68.8%)	40 (81.6%)	42 (97.7%)
Week 48				
n	36	16	49	42
≥ 90% improvement	3 (8.3%)	2 (12.5%)	11 (22.4%)	7 (16.7%)
≥ 75% improvement	17 (47.2%)	7 (43.8%)	25 (51.0%)	22 (52.4%)
≥ 50% improvement	29 (80.6%)	12 (75.0%)	40 (81.6%)	38 (90.5%)
Week 52				
n	35	16	48	43
≥ 90% improvement	5 (14.3%)	2 (12.5%)	11 (22.9%)	8 (18.6%)
≥ 75% improvement	15 (42.9%)	5 (31.3%)	25 (52.1%)	19 (44.2%)
≥ 50% improvement	28 (80.0%)	12 (75.0%)	39 (81.3%)	38 (88.4%)
Week 56				
n	29	11	32	32
≥ 90% improvement	7 (24.1%)	1 (9.1%)	8 (25.0%)	5 (15.6%)
≥ 75% improvement	14 (48.3%)	6 (54.5%)	16 (50.0%)	15 (46.9%)
≥ 50% improvement	25 (86.2%)	9 (81.8%)	25 (78.1%)	25 (78.1%)

Source: Sponsor's attachment 3.39 from the report c0743t08-report-body-52wk.pdf (Pages 383-385 of 1250)

Are the labeling claims based on population pharmacokinetic model acceptable?

- No pharmacokinetic data are available in patients with hepatic or renal impairment.
- A population pharmacokinetic analysis indicated there were no apparent changes in pharmacokinetic parameters in patients > 65 years.
 - The claim is acceptable. Body weight is the major pharmacokinetic covariate. There were 1831 (94.5%) subjects < 65 years of age and 106 (5.5%) subjects ≥ 65 years of age (elderly) in the combined dataset. The sponsor evaluated potential effects of age on CL/F and V/F of ustekinumab in covariate model building. The effect of age on CL/F and V/F was not significant.

Figure 15: Ustekinumab CL/F by age group in subjects with psoriasis



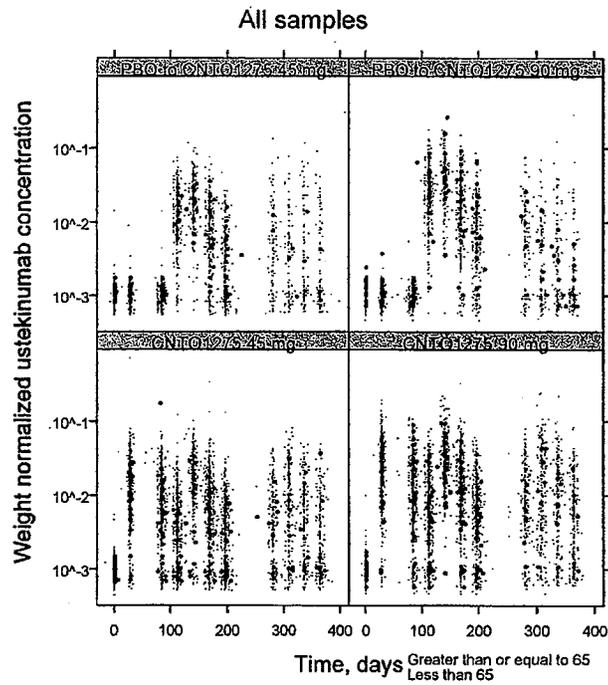
Source: Sponsor's figure 7 from the report summary-clin-pharm.pdf (Page 42 of 80)

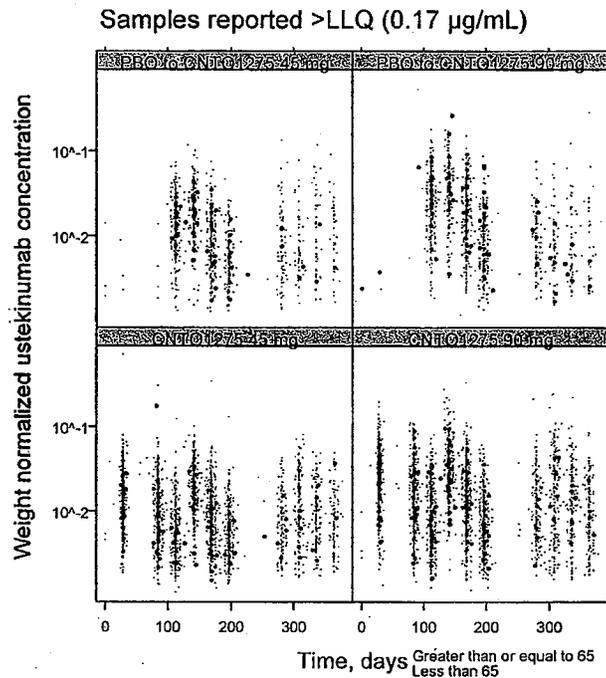
The reviewer's analysis based on empirical concentration data resulted in consistent results with the sponsor's conclusion. It included 2 more subjects in age group ≥ 65 years.

Table 11: Number of subjects (Number of samples) included in the following figure.

	Greater than or equal to 65	Less than 65
	Number of subjects (Number of blood samples)	
CNT01275 45 mg	29(216)	634(4918)
CNT01275 90 mg	37(266)	629(4878)
PBO to CNT01275 45 mg	20(148)	300(2390)
PBO to CNT01275 45 mg	22(177)	292(2328)

Figure 16: Ustekinumab concentration (weight normalized) over time from sparse sampling. The data are stratified by age (<65 years: red and ≥ 65 years: black).





- Serum ustekinumab concentrations were affected by patient weight. When given the same dose, patients of higher weight (> 100 kg) had lower median serum ustekinumab concentrations compared with those in patients of lower weight (≤ 100 kg).
 - The claim is reasonable (see Body weight-ustekinumab concentration relationship). However, the sponsor is recommended to add quantitative information to interpret information clearly.

Appendices

Appendix I: Clinical Pharmacology Question Based Review (Pharmacometrics component: for Clinical Pharmacology Reviewer)

2. Question based review

2.1. General Attributes

NA

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the pivotal clinical trials?

See Data section of pharmacometrics review for design features of PHOENIX I (PHOENIX 1) and PHOENIX II (PHOENIX 2)

2.2.2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Body surface area (BSA) and Psoriasis Area and Severity Index (PASI) score, which combines the extent of psoriasis with local skin signs (erythema, scale and elevation), have been the most frequently used to assess psoriasis severity. Physician's global assessment (PGA) of psoriasis severity has been used as a global static assessment of all lesions on 6- or 7-point scale (from severe to none); it gives a general impression of severity or improvement of psoriasis on treatment.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Serum ustekinumab concentrations were measured using a validated ELISA with a LLOQ of 0.08 µg/mL following a 1:10 dilution. For phase III studies, Serum ustekinumab concentrations were measured using a validated electrochemiluminescent immunoassay (ECLIA), which was capable of quantifying a serum ustekinumab concentration with a LLOQ of 0.17 µg/mL.

2.2.4. Exposure-response evaluations

2.2.4.1. What are the characteristics of the exposure-response relationship for efficacy?

Serum ustekinumab concentrations were associated with clinical response. Subjects with higher median serum concentrations of ustekinumab generally had greater clinical responses, as measured by PASI response, than subjects with lower median serum concentrations of ustekinumab. For example, the PASI75 response rate at week 12 in 135 subjects that had undetectable serum ustekinumab concentrations was 37% as measured by PASI75. The response rate increased to 75% in subjects with median concentrations ≥ 0.9 µg/mL. See pharmacometrics review (section: Does exposure response analysis support evidence of effectiveness?) for more details.

2.2.4.2. What are the characteristics of the exposure-response relationship for safety?

The major (biologically potential) safety concern for ustekinumab was carcinogenicity due to its mechanism of action by blocking IL-12 and IL-23 expression. Also, there was no obvious dose dependent pattern in overall adverse events (AE), serious AEs, discontinuations due to AE or death. No apparent pattern to type of malignancies was observed through 18 months of follow up (source: Dr. Carr's advisory committee presentation). Due to the lack of obvious signals, exposure-safety analysis was not conducted. See pharmacometrics review (section: Are there any exposure related safety concerns?) for more details.

2.2.4.3. Does this drug prolong the QTc interval?

NA

2.2.4.4. Are the dose and dosing regimen of ustekinumab consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed dosing recommendations for ustekinumab by the sponsor were:

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

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

The AUC-PASI75 response rate model was used to explore alternate dosing regimens, such as one dose for all (45 or 90 mg) and several weight based dosing regimens. The aim was to derive a regimen that might yield optimal PASI75 response rate for entire population. According to the observed data as well as model predictions, a 45 mg dose is suboptimal in higher body weight subjects and a 90 mg dose does offer higher benefit in these subjects.

The key findings from exploring alternative dosing regimen were:

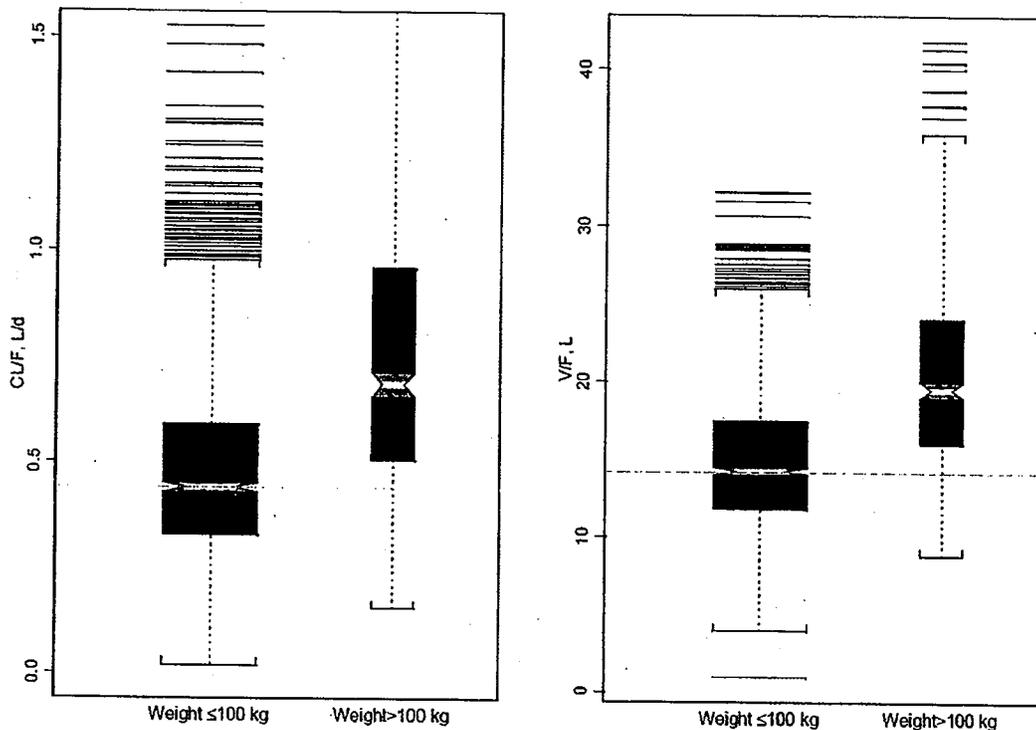
- PASI75 response rate can be further maximized by weight based adjustment.
 - Administration of ustekinumab based on two step body weight cut off (100 kg) increases the overall response rate to 70% with the gains in heavier subjects.
 - Administration of ustekinumab based on 3 step body weight cut offs (<70, ≥70-<100 and ≥100 kg) or 5 step body weight cut offs (<45, ≥45-<60, ≥60-<75, ≥75-90 and >90 kg) or semi-continuous (mg/kg) weight based dosing could yield PASI75 response rate comparable to administration of 90 mg to all subjects (overall 75%).
- None of the body weight based adjustments will yield AUCs in excess of those observed after 90 mg administration. All predictions are within the observed AUC ranges.
- In the same order the necessity of accurate dose calculation seem to increase.
- These data were presented to the advisory committee (<http://www.fda.gov/ohrms/dockets/ac/cder08.html#DermatologicOphthalmicDrugs>) on June 17, 2008, the two step dosing proposal was recommended by 7 votes vs 3 votes for three step dosing proposal.
 - The main concerns from the committee were
 - Lack of data at 67.5 mg
 - Possible delays in generating stability data for 67.5 mg
 - Lack of availability of information on the lowest effective dose
- Finally, each of the dosing strategies explored here offer different advantages. In reviewer's opinion, all the concerns above can be alleviated through objective discussions. Because the perceived benefit needs to be clinically justified, the reviewer found the discussion at advisory committee meeting useful. The open public hearing added to the gravity of psoriasis in social setting, thus maximizing responder rate should be the goal of these therapies. Based on increased benefit and lack of any exposure related safety concerns, the reviewer recommends three step dosing regimen.

See pharmacometrics review (section: Based on exposure response analysis, is the sponsor's dosing proposal acceptable?) for more details.

2.3. Intrinsic Factors

2.3.1. What intrinsic factors influence exposure or response to ustekinumab? What is the impact of these factors on exposure and response?

Body weight is the major intrinsic factor affecting ustekinumab exposure and response. See Pharmacometrics review (section: Body weight-proportion of PASI75 responders relationship). The change in CL/F due to body weight was from -12% to +11% of the median CL/F estimate when body weight increased from 25 percentile (76.0 kg) to 75 percentile (103.5 kg) of the subject values. The change in V/F due to body weight was from -11% to +11% of the median V/F estimate when body weight increased from 25 to 75 percentile of the subject values. The comparison of CL/F and V/F between heavier (>100 Kg) and lighter subjects (≤100 Kg) is provided below. Median CL/F and V/F values were 0.44 L/d and 14.2 L, respectively, in subjects with body weight ≤100 Kg; and were 0.68 L/d and 19.5 L, respectively, in subjects with body weight >100 Kg. This represents approximately 55% higher CL/F value and 37% higher V/F value in subjects with body weight >100 Kg as compared to the respective values in subjects with body weight ≤100 Kg.



Source: Sponsor's figure 5.6.1 from the report pop-pk.pdf (Page 55 of 456)

Other factors that affect pharmacokinetics of ustekinumab are diabetes comorbidity and positive immune response to ustekinumab. There were 206 subjects (10.6%) with diabetes comorbidity included in the population analysis using combined dataset from both studies. The model-predicted mean CL/F and V/F values for ustekinumab were 28.7% and 13.2%, respectively, higher in subjects with diabetes.

There were 62 subjects (3%) in the combined dataset who developed positive immune response to ustekinumab over the course of treatment with ustekinumab. The model-predicted mean CL/F value for ustekinumab was 35.5% higher in subjects with positive immune response to ustekinumab than that in subjects with other immune responses (i.e., negative or undetectable). The increased CL/F and reduced systemic exposure of CNTO 1275 in subjects with positive immune response is consistent with the neutralizing effect of antibodies present in the systemic circulation in majority of these subjects. However, with only a small number of subjects who developed positive immune response in both studies.

The impact on PASI75 response of differences in ustekinumab exposure due to diabetes co-morbidity was evaluated. In the data relevant to the proposed dosing recommendations (45 mg for <100 kg subjects and 90 mg for ≥100 kg), the proportion of PASI75 responders was lower in subjects with diabetes history or existing condition. For example, 59.5% (N=37) vs 75.5% (N=421) at 45 mg for <100 Kg and 65.5% (N=29) vs 73.1% (N=193) at 90 mg for ≥100 kg. The response rate in all subgroups was at least 60%, however, the number of subjects with diabetes were less to interpret precise differences. Higher difference was seen in 45 mg group for <100 kg subjects, the recommended 3 step dosing proposal might reduce these differences as patients with diabetes will receive 67.5 mg leading to higher ustekinumab levels. Thus, dosing change based on diabetes co-morbidity is recommended at this time.

2.3.2. Based on what is known about exposure-response relationships, what dosage regimen adjustments, if any, are recommended for each subgroup listed below?

2.3.2.1. Elderly

No dose adjustment is necessary. See Pharmacometrics review (section: Are the labeling claims based on population pharmacokinetic model acceptable?)

2.3.2.2. Pediatric Patients

According to the proposed label, the sponsor claims safety and effectiveness in pediatric patients have not been established.

2.3.2.3. Gender

No dose adjustment is necessary.

2.3.2.4. Race

No dose adjustment is necessary.

2.3.2.5. Renal Impairment

According to the proposed label, the sponsor claims no pharmacokinetic data are available in renal impairment.

2.3.2.6. Hepatic impairment

According to the proposed label, the sponsor claims no pharmacokinetic data are available in hepatic impairment.

2.4. Extrinsic factors

2.4.1. What are the extrinsic factors that influence exposure or response?

The sponsor did not conduct in vitro metabolic-based drug-drug interaction studies using human hepatocytes or hepatic microsomes for ustekinumab. However, potential drug-drug interactions were investigated in a population PK analysis using data from the 2 Phase 3 studies. A total of 28 most frequently used concomitant medications were evaluated for potential drug-drug interactions. For more details refer to pharmacometrics review- section: Appendix II: Population Pharmacokinetics analysis. None of the concomitant medications had a significant effect upon the CL/F of ustekinumab. However, there are no data available on effect of ustekinumab on metabolism of other drugs.

Appendix II: Population Pharmacokinetics analysis

Sponsor's analysis

A one-compartment PK model with first-order absorption and first-order elimination was used as the structural PK model to describe the serum concentration vs. time data of ustekinumab following SC injections in subjects with psoriasis. Based on the structural model, a population PK analysis was performed using serum concentration-time data of ustekinumab collected through Week 28 from the first-available Phase 3 study (C0743T09) in subjects with psoriasis. After the population PK model was developed, data collected through Week 52 from another Phase 3 study (C0743T08) in subjects with psoriasis were used as an external validation data set to validate the population PK model developed based on Study C0743T09. Upon successful completion of external validation, final population PK analysis was performed using combined serum concentration-time data from both studies to improve precision of the PK parameter estimates of ustekinumab in the population PK model.

Table 12: Population pharmacokinetic parameters (Population Mean ± SE [RSE%]) of CNTO 1275 from the Final Model Using Combined Data from Studies C0743T09 and C0743T08

Parameters	Estimate ^a	BSV (%) ^b	Magnitude of Change
CL/F (L/d) ^c	0.465 ± 0.009 (2.0%)	41.0% (3.0%)	-
V/F (L) ^c	15.7 ± 0.31 (2.0%)	33.2% (3.9%)	-
ka (1/d)	0.354 ± 0.057 (16%)	0 fixed	-
WT on CL/F ^d	0.840 ± 0.055 (6.5%)	-	-12% to +11% ^f
IRP on CL/F ^d	0.355 ± 0.047 (13%)	-	35.5% increase in positive IR
DIAB on CL/F ^d	0.287 ± 0.041 (14%)	-	28.7% increase in diabetes
ALB on CL/F ^d	-0.896 ± 0.106 (12%)	-	-2.3% to +7.7% ^f
CRCL on CL/F ^d	0.188 ± 0.030 (16%)	-	-4% to +4% ^f
SEX on CL/F ^d	0.059 ± 0.016 (28%)	-	5.9% increase in females
ALK on CL/F ^d	0.113 ± 0.025 (22%)	-	-2% to +1.2% ^f
WT on V/F ^e	0.807 ± 0.049 (6.1%)	-	-11% to +11% ^f
DIAB on V/F ^e	0.132 ± 0.042 (32%)	-	13.2% increase in diabetes
RGP on V/F ^e	-0.111 ± 0.026 (23%)	-	11% decrease in non-Caucasians

Source: Attachment 39.1 and Appendix 5.2.
 Proportional residual error 25.6 %
^a Parameter precision is expressed as ± standard error (SE) and relative SE (RSE% = [SE ÷ mean] * 100%).
^b BSV = between subject variability calculated as (variance)^{1/2} * 100%; the precision of variance is expressed as RSE%
^c Correlation between CL/F and V/F is 0.817, calculated as covariance₁₂ ÷ (variance₁ * variance₂)^{1/2}, where variance₁ and variance₂ are variances of random effects for the two parameters and covariance₁₂ is their covariance
^d CL/F = 0.465 • (WT/90)^{0.84} • (ALB/4.5)^{-0.90} • (CRCL/120)^{0.188} • (ALK/80)^{0.12} • (1 + 0.287*DIAB) • (1 + 0.355*IRP) • (1 + 0.059*SEX) L/d
^e V/F = 15.7 • (WT/90)^{0.807} • (1 - 0.111*RGP) • (1 + 0.132*DIAB) L
^f The magnitude of change in the parameter estimate caused by a continuous variable was expressed as a range, i.e., % change from the median value when the continuous covariate factor varied from 25 percentile to 75 percentile of the population.
^g Abbreviations: BSV = between subject variability; WT= body weight; IRP= positive immune response to CNTO 1275; DIAB= diabetes comorbidity; ALB= albumin; CRCL= creatinine clearance; ALK= alkaline phosphatase; RGP= race group

The sponsor developed a one-compartment population PK model ustekinumab in subjects with psoriasis in 2 Phase 3 studies to identify factors that could contribute to the variability in the systemic exposure of ustekinumab in subjects with psoriasis. Of the demographic factors (eg, gender, race, age, body size) baseline subject physical or biochemical characteristics, or medical or medical history, or concomitant medications (total of 28), evaluated in the population PK analysis, only subject weight, comorbidity of diabetes, and positive immune response to ustekinumab were found to be important covariates affecting the systemic exposure to ustekinumab in subjects with moderate to severe psoriasis. See the sponsor's report pop-pk.pdf for more details.

The NM-TRAN Control Stream and the Abbreviated and Full NONMEM Output for the Final Model Using the C0743T09 and C0743T08 Combined Data (source: Sponsor's Appendix 5.2 from the report pop-pk.pdf (Pages 282-307 of 456)).

Appendix 5.2

The NM-TRAN Control Stream and the Abbreviated and Full NONMEM Output for the Final Model Using the C0743T09 and C0743T08 Combined Data

b(4)

Note:

The abbreviated NONMEM output was generated by █████ for NONMEM.

The first block listed the THETA, ETA and SIGMA parameter names, the second block listed their estimates and the third block listed their standard errors of estimates.

24 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Reviewer's analysis

The sponsor's analysis was reproduced and similar results as described above were obtained. The focus of reviewer's analysis was to establish and further evaluate relationship between ustekinumab pharmacokinetics and body weight. Data from 335 subjects (17 from C0379T02 and 318 from C0379T04) were used the analysis. The following tables provides summary of NONMEM runs.

Run No	Description	OFV	dOFV	Significant Digits	Warnings
1	One compartment PK model: Base model	4816.767	0	4.1	Large SEs (Sg 1)
2	Base model + combined error model	2505.246	2311.521	4.5	
3	Run 2 + weight effect on CL/F (allometric model)	2496.791	8.455	5.1	
4	Run 2 + weight effect on V/F (allometric model)	2491.706	5.085	4.9	

Run 1 summary

Observation records: 2061
Individuals: 335
Condition number: Not available
Model type: One Compartment Model With First-Order Absorption (ADVAN2)
Minimization: Successful

Fixed effects

Theta	Value	SE (RSE)
1 CL/F (Th1)	0.351	0.0147 (4.19)
2 V/F (Th2)	14.8	0.746 (5.04)
3 KA (Th3)	0.467	0.0496 (10.6)

Interindividual variability

Eta	Value	SE (RSE)
(Eta1)	0.174	0.0349 (20.1)
(Eta2)	0.239	0.0346 (14.5)
(Eta3)	0.366	0.102 (27.9)

Residual variability

Epsilon	Value	SE (RSE)
Eps1	2.96	1.1 (37.2)

Warnings

Large SEs (Sg 1)

Model

\$PROBLEM STUDY0204 DATA- ONE COMPARTMENT MODEL- BASE MODEL
\$INPUT ID TIME DV WT SEX RACE AMT MDV STUD

3 Page(s) Withheld

Trade Secret / Confidential (b4)

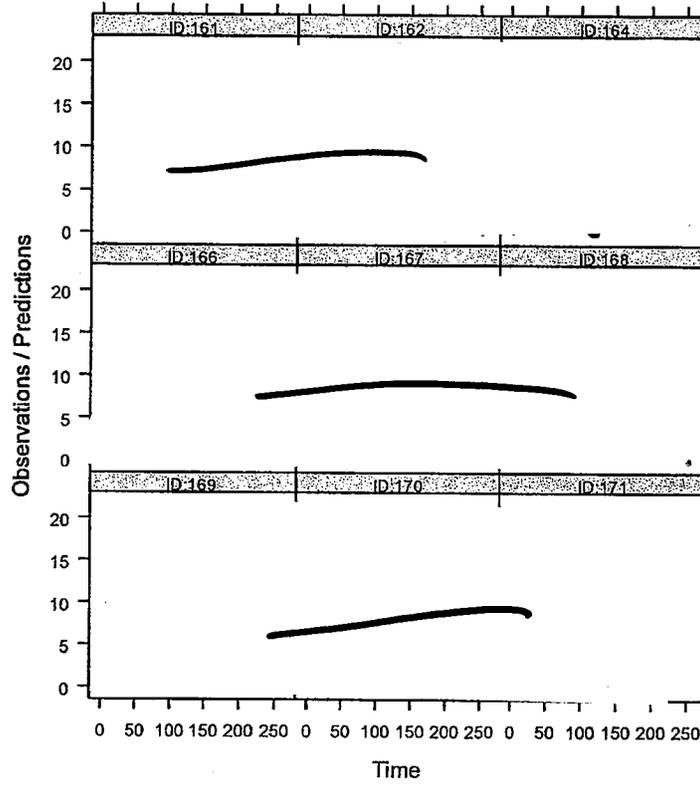
Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Individual plots (Run 4)

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b(4)

9 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

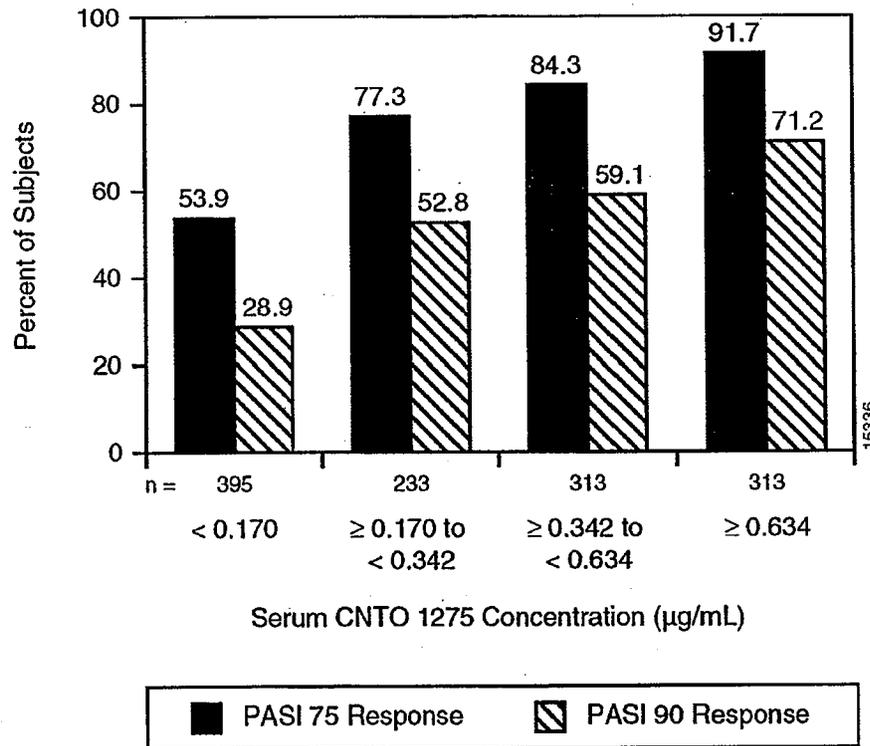
 Deliberative Process (b5)

Appendix III: Exposure (ustekinumab AUC)- response (PASI75 and PGA) analysis

Sponsor's analysis

Dose-dependent improvement in PASI was generally observed with a greater degree of PASI improvement and duration of response seen in the higher dose groups in Phase 1 and Phase 2 studies (C0379T01, C0379T02, C0379T04). Overall, serum ustekinumab levels were associated with clinical response. Subjects with higher median serum concentrations of ustekinumab generally had greater clinical responses, as measured by PASI response, than subjects with lower median serum concentrations of ustekinumab. The proportion of subjects who achieved PASI 75 or PASI 90 responses at Week 28 increased with increasing trough serum ustekinumab levels.

Figure 17: Percent of subjects achieving PASI75 and PASI90 responses at Week 28 by trough serum ustekinumab concentrations at Week 28 in psoriasis Phase 3; treated subjects randomized to ustekinumab at Week 0



Based on the distribution quartiles of the serum concentration data, the trough serum concentrations at Week 28 for subjects randomized to ustekinumab were divided into 4 ranges: < 0.170 µg/mL; ≥ 0.170 to < 0.342 µg/mL; ≥ 0.342 to < 0.634 µg/mL; and ≥ 0.634 µg/mL. The number (n) is given below each range. All serum ustekinumab samples below the LLOQ were categorized as < 0.170 µg/mL.

Source: Sponsor's figure 13 from the report summary-clin-pharm.pdf (Page 50 of 80)

Reviewer's analysis

The effect of ustekinumab exposure and several other predictors on the PASI and PGA response was analyzed as a binary variable (PASI75 and PGA cleared or minimal) using both logistic regression and generalized additive models (GAM). A GAM model was built using the automated step-wise search developed in S-PLUS. This automated step-wise search selects the best GAM using forward selection and backwards deletion given the range of models. A series of candidate relationships (e.g. linear, log-transformation, spline, Loess smooth) that describe how each particular predictor might enter the model was defined for every predictor and the final model was built up by evaluating all candidate forms for each predictor in a step-wise manner based on AIC value.

Clinical data obtained up to week 12 in 1947 subjects from two studies (PHOENIX I and II) were used for the analysis. There were n=650 (45 mg) and n=646 (90 mg) ustekinumab treated subjects. The models were investigated using ustekinumab AUC, weight, age, sex and race as predictors of the response.

Table 13: GAM models at the end of automated step-wise search for prognostic factors of PASI75 and PGA response

Model	Endpoint	Parameter included in the analysis	GAM model	Comment
1	PASI75 at 12 weeks	AUC (AUC.imp)	pasi75.n ~ lo(AUC.imp) + log(weight) + age + sex + race	Final model
2	PGA at 12 weeks	AUC (AUC.imp)	pgamin.n ~ lo(AUC.imp) + log(weight) + sex	Final model

Figure 18: Results of the automated step-wise GAM search for prognostic factors of PASI75 (Model 1) and PGA (Model 2). On the y-axis, "-> a" indicates addition of variable "a"; "a->b" indicates the replacement of variable "b" with "a".

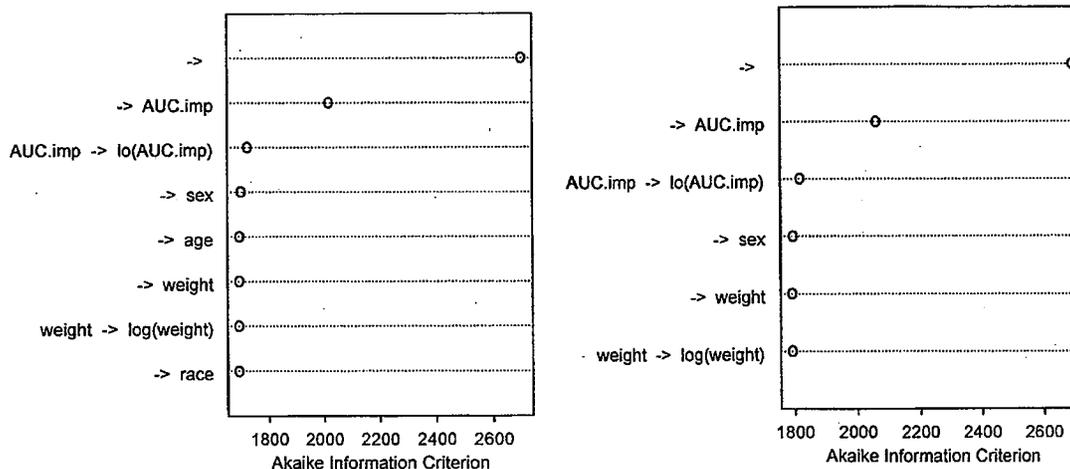
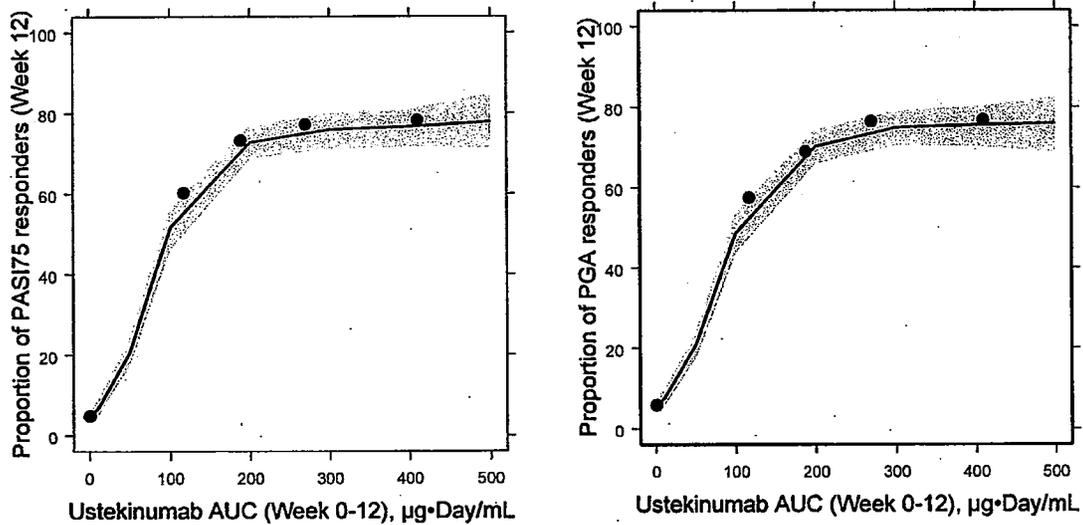


Figure 19 shows the median (95% CI) prediction of percentage of responders (PASI75 and PGA) as a function of the ustekinumab AUC. The results show that the predicted likelihood of response increases when exposure to ustekinumab increases. Simulations of exposure-proportion of responders defined as PASI75 and PGA relationships including model uncertainty (but not the residual error) were performed. Ustekinumab AUC values covering the observed exposure range were assigned to each subject in the original database while keeping all other data as it was originally recorded. The likelihood of response was subsequently predicted based on the corresponding 300 sets of GAM parameters obtained in a bootstrap step. The calculated median and 95% confidence interval for the predictions from the replicates were presented graphically, as a function of ustekinumab exposure.

Figure 19: Median (95% CI) prediction of likelihood of response (PASI75 and PGA) as a function of ustekinumab AUC, based on the GAM models fitted to 300 bootstrap samples of the original data set. (circles: observed data, line and shaded area: model prediction)



PHARMACOGENOMICS REVIEW

BLA: STN 125261/0
Drug Name: Ustekinumab
Indication: Moderate to severe psoriasis
Genomics reviewer: Shashi Amur, Ph.D. and Padmaja Mummaneni, Ph.D.
Applicant: Centocor

1. EXECUTIVE SUMMARY

Psoriasis vulgaris is a complex disorder that is characterized by inflammation and keratinocyte hyperproliferation. The etiology of the disease is not completely understood. However, the available evidence suggests that Type 1 helper cells (Th1), macrophages and certain cytokines play a major role in the pathogenesis of the disease. In a murine psoriasis disease model, interleukin (IL)-12 appears to be involved in the pathogenesis of a psoriasis-like skin disorder since a neutralizing antibody to IL-12 could abolish the psoriasiform lesions. These studies suggested that neutralizing antibodies to IL-12 could have therapeutic potential in the treatment of psoriasis.

Ustekinumab (CNTO 1275) is a fully human monoclonal antibody to human IL-12p40, which binds to human or primate IL-12 and IL-23 with high affinity. The antibody binds to the shared p40 subunit of IL-12 and IL-23 and prevents binding to the IL-12R β 1 receptor. Thus, Ustekinumab may block the signaling events and cytokine cascades that follow the binding of IL-12 and IL-23 to the IL-12R β 1 receptor.

Three exploratory studies have been submitted, in addition to a publication in the Journal of Immunology. Two of the exploratory studies employed cDNA microarray technology to identify potential biomarkers of efficacy of CNTO 1275. Additionally, an attempt was made to identify the mechanism of action of the drug and to understand the molecular underpinnings of the pathological process involved in psoriasis. The microarray data assisted in the identification of potential biomarkers for the efficacy of CNTO 1275. Since the microarray data is of exploratory nature and yields a number of false positives, potential biomarkers need to be verified using other technologies such as quantitative real time RT-PCR.

The PCR data obtained with limited number of samples, suggests a correlation of reduced levels of some inflammatory cytokines and chemokines with CNTO 1275 treatment. However, placebo was not used as a comparator in this study and the consistency of these findings was not tested in more than one exploratory study. The exception is IL-12p40 mRNA. In two of the studies, a significant reduction in

the IL-12p40 mRNA has been reported with CNTO 1275 treatment. However, statistically significant difference in the IL-12p40 mRNA levels was not observed in the third study that examined the samples at week 0 and week 12.

In conclusion, exploratory biomarkers for CNTO 1275 efficacy have been identified in the studies.

2. RECOMMENDATIONS

We recommend that the sponsor continues the search for efficacy biomarkers in the context of CNTO 1275 with emphasis on reproducibility of the findings and correlation to the clinical end point. Early identification of non-responders through the use of biomarkers would benefit the clinicians and patients.

If the sponsor opts to get scientific advice from FDA on exploratory data that are not required to be submitted as an IND, it is possible to use the voluntary exploratory data submission (VXDX) process. Please refer to <http://www.fda.gov/Cder/guidance/6400fnl.pdf>
<http://www.fda.gov/Cder/guidance/6400fnlAttch.pdf>

For qualification of biomarkers (disease or diagnostic biomarkers/efficacy- or safety-related biomarkers, a pilot process for biomarker qualification is also available.

3. SUMMARY OF GENOMICS DATA

Clinical studies submitted with gene expression data: Three studies were submitted that contained gene expression data: Phase I CSR C0379T01, C0379T02 and Phase II CSR C0379T04. In addition, a publication was also submitted to support the findings from the studies.

a. Summary of study CSR C0379T01:

The primary objectives of this Phase I, first-in-human trial were to establish the short-term safety, tolerability, and pharmacokinetic profiles of single, ascending, intravenous (IV) administrations of CNTO 1275 in subjects with moderate to severe psoriasis vulgaris. One of the secondary objectives of this study was to assess the pharmacodynamics response to single, ascending, IV administrations of CNTO 1275 in subjects with moderate to severe psoriasis vulgaris.

Study subjects: A total of 18 subjects were enrolled and treated: 4 subjects were dosed with CNTO 1275 at 0.09 mg/kg, 4 subjects at 0.27 mg/kg, 5 subjects at 0.9 mg/kg, and 5 subjects 4.5 mg/kg.

Methodology: Total ribonucleic acid (RNA) was extracted from one half of a 6-mm punch biopsy from patients in each of the 4 indicated dose groups obtained at baseline, 48 hours and 2 weeks post-treatment. Total RNA was obtained using an RNeasy midi kit following tissue pulverization in a mikro dismembrator.

Quantitative real time PCR reactions were carried out utilizing the Taqman technology. Copy numbers of samples were calculated against input copy numbers of plasmid standards for each target gene and normalized with the copy numbers of housekeeping gene 18SrRNA. Cytokines examined were: IL-12p40, IL-12p35, IL-18, IL-8, RANTES, monocyte chemotactic protein 1 (MCP-1), IFN γ , tumor necrosis factor (TNF), and interferon-inducible protein 10 (IP-10).

Results:

As shown in Table 7 below, a decrease in mRNAs for IFN γ , IL-12p40, IL-10, IL-8, TNF- α and IP-10 was observed for all the doses examined at two weeks.

Table 7 Percent change from baseline in cytokine level

Cytokine	0.1 mg/kg		0.3 mg/kg		1.0 mg/kg		5.0 mg/kg	
	2 Days	2 Weeks						
IL-12p40	-19	-71	-8	-65	15	-66	9	-64
IL-12p35	-23	18	17	34	10	27	8	58
IL-8	-69	-98	-38	-90	-19	-89	-83	-43
IL-18	-15	10	8	-15	16	12	3	-1
TNF α	-22	-29	3	-23	-21	-49	36	10
RANTES	-25	-55	28	-11	11	-37	67	33
IP-10	-24	-68	-15	-69	39	-61	115	-16
IFN γ	-25	-67	-25	-63	-2	-65	-2	-44
MCP-1	-42	-42	35	-45	1	-47	48	-13
IL-10	-39	-74	29	-69	-19	-70	-24	-50

Comments:

The number of samples was very small (4 subjects were dosed with CNTO 1275 at 0.09 mg/kg, 4 subjects at 0.27 mg/kg, 5 subjects at 0.9 mg/kg, and 5 subjects 4.5 mg/kg) and the study is exploratory. Information on the reproducibility of the data and variability of the mRNA levels between the treated individuals is not provided.

b. Summary of study CSR C0379T02:

The primary objectives of the study were to assess the safety and pharmacokinetics of single SC administrations of CNTO 1275 in subjects with psoriasis vulgaris. One of the secondary objectives of the study was to assess the pharmacodynamics response of single SC administrations of CNTO 1275 in subjects with psoriasis vulgaris.

Study subjects:

A total of 21 subjects were enrolled, treated, and analyzed (5 subjects were dosed with 0.27 mg/kg, 4 subjects were dosed with 0.675 mg/kg, 4 subjects were dosed

with 1.35 mg/kg, 4 subjects were dosed with 2.7mg/kg, and 4 subjects were dosed with placebo).

Methodology:

The microarray chip technology analysis of mRNA expression and the TaqMan® PCR analysis both have the potential to identify additional biological markers and were considered exploratory methods to identify preliminary effects of CNTO 1275.

Microarray analysis

mRNA quality and quantity were analyzed with the Agilent 2100 bioanalyzer. Duplicate chips were used for each RNA sample. Non-linear normalization between duplicate chips allowed each clone to be averaged to a single intensity value for each RNA sample.

TaqMan® PCR analysis

To measure IL-12-related genes that are not included on the microarray chip (ie, IL-12p40), it was necessary to perform TaqMan® PCR analysis. Expression levels were normalized to mRNA levels of the housekeeping gene (GAPDH). IL-12p40 expression was calibrated to the placebo group at each timepoint and the gene expression at week 1 was compared to day 0. Modulation in gene expression was measured as the percent change after administration of study agent, relative to day-0 levels.

Results:

The IL-12-related genes in the skin biopsy samples that exhibited a change in gene expression in the microarray experiments are shown in the table below:

Table 14 Microarray analysis of IL-12 related genes in skin biopsies post study drug treatment

Treatment Group	Common Name	Fold Change	P-value	Gene Bank #	Description
Up-regulated					
0.75 mg/kg		1.589	0.04757		
		1.497	0.02103		
Down-regulated					
0.3 mg/kg		2.528	0.02508		
		1.859	0.04476		
0.75 mg/kg		2.660	0.03367		
		2.639	0.01717		
		2.556	0.04786		
		2.162	0.01887		
		1.748	0.03877		
3.0 mg/kg		1.510	0.03968		
		1.640	0.03124		
		1.658	0.03911		
		1.755	0.04176		
		2.026	0.04103		

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However, no statistical differences in gene expression could be discerned when multiple test correction was applied.

The expression of IL-12p40 was examined with Taqman PCR and a decrease in the gene expression was noted in the patients treated with CNTO 1275 (no data shown).

Comments:

As in the previous study, the sample size was small. In addition, as the applicant suggests, these data are of exploratory nature and the decreases in gene expression observed in the microarray analysis were not statistically significant upon applying multiple test correction.

c. Summary of study CSR C0379T04:

CSR C0379T04 Phase II, Randomized, Double-blind, Placebo-controlled, Parallel Study of Single and Multiple Dose Regimens with Subcutaneous CNTO 1275 in Subjects with Moderate to Severe Psoriasis. One of the secondary objectives was to assess the pharmacodynamics of single and multiple SC injections of CNTO 1275 in psoriasis subjects by measurement of relevant biomarkers in serum, whole blood, and tissue biopsies.

The gene expression analysis was conducted to identify potential biomarkers of CNTO1275 efficacy and to better understand the mechanism of action of CNTO1275 and also to understand the pathological mechanisms underpinning psoriasis.

Study subjects:

300 subjects will be enrolled (60 subjects per group).

Group I: CNTO 1275 50 mg on day 1 (week 0) and placebo at weeks 1, 2, and 3. At week 16, subjects with PGA \geq 3 will receive CNTO 1275 50 mg. Subjects with PGA < 3 will receive placebo. At week 20, all subjects will receive placebo to maintain the blind.

Group II: CNTO 1275 100 mg on day 1 (week 0) and placebo at weeks 1, 2, and 3. At week 16, subjects with PGA \geq 3 will receive CNTO 1275 100 mg.

Group III: CNTO 1275 50 mg on day 1 (week 0) and at weeks 1, 2, and 3.

Group IV: CNTO 1275 100 mg on day 1 (week 0) and at weeks 1, 2, and 3.

Methodology:

RNA Extraction

A total of 74 RNA samples were prepared from 74 skin biopsy samples obtained from 38 subjects. 54 RNA samples from 34 subjects were used for the DNA microarray analysis.

Microarray Chip Processing

A cDNA microarray containing 8159 human gene cDNA clones was used in this analysis. Duplicate chips were used for each RNA sample generating 4 technical replicates for each clone. Non-linear normalization between duplicate chips

allowed each clone to be averaged to a single intensity value for each RNA sample.

Quantitative Real-time RT-PCR (TaqMan®) Analysis

Of the genes that showed at least a 1.5-fold change from baseline in mRNA expression levels by microarray analysis, TaqMan® PCR was used as an independent method to validate the changes in mRNA expression of selected genes. Seventeen paired samples (baseline at Week 0 and Week 12) corresponding to 34 RNA samples were available for TaqMan® PCR analysis. The expression level of the housekeeping gene glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used to normalize samples. Based upon results of the microarray analysis and the mechanism of action of CNTO 1275, the 10 genes selected for further analysis were SERPINB3, SERPINB4, GJB2, IL-1F9, STAT1 (signal transducer and activator of transcription), KIAA0014, IL-12/23 p40, IL-12 p35, IL-23 p19 and TNFRSF5. The mRNA levels of SERPINB3, SERPINB4, GJB2, IL1F9, STAT1, and KIAA0014 were determined for all 17 pairs of RNA samples as these genes were identified by the microarray analysis.

Results:

39 samples from 25 subjects were analyzed by the cDNA microarray. Among these samples, only 34 samples from 17 subjects were further analyzed by TaqMan® PCR due to limitations in the quantity of available RNA.

Microarray data analysis: Because of small sample size in each dose group, combined data for the two 90 mg dose groups (single and multiple doses), and combined data for the nonresponders were used to identify differentially expressed genes.

A listing of significantly (p-value of < 0.05) differentially regulated mRNAs from the combined 90 mg treatment responder group compared with baseline is shown in the table below:

Attachment 5 Significantly differentially regulated 12 genes for the combined 90 mg treatment PASI 75 responder group compared to placebo group at Week 12

Gene ID	Fold Change	Gene name	Genbank ID	Description
	-2.27			
	-1.86			
	-1.80			
	-1.69			
	-1.66			
	-1.58			
	-1.58			
	-1.56			
	-1.52			
	-1.52			
	-1.52			
	-4.16			

*.25 sign indicates down-regulation. A blank entry in the Gene name column and Description column indicates an unknown gene.

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Quantitative Real-time RT-PCR (TaqMan®) Results

Since no statistical differences in gene expression could be detected when the multiple test correction was enforced, genes could have been identified by chance by the microarray analysis.

Therefore, quantitative real time reverse transcription polymerase chain reaction (qRT-PCR or TaqMan® PCR) analysis was used as an independent validation method. A 2-sided T-test was conducted on the paired RNA samples between Week 0 and Week 12 at a significance level of 0.05. Four genes (SERPINB3, SERPINB4, GJB2 and IL1F9) were significantly ($p < 0.027$) down regulated in the 90 mg dose responder (> 75% improvement in PASI score from baseline) groups confirming the results of the microarray analysis. TaqMan® PCR analysis of KIAA0014 and TNFRSF5 did not support the results obtained by microarray indicating some that the microarray analysis generated some false positive results. This was not an unexpected finding given the small samples size of this study. Since cDNAs for the various subunits of IL-12 or IL-23 were not included on the microarray chip, mRNA levels for these genes were assessed using TaqMan® PCR analysis. Although none of the changes reached statistical significance, IL-23 p19 mRNA levels were decreased, and IL-12 p35 mRNA levels were increased after CNTO 1275 treatment.

Conclusions:

As the applicant notes in the conclusions section “Due to an insufficient number of samples, no conclusion could be made regarding changes in IL-12/23 p40 mRNA levels. Overall, the limited amounts of RNA obtained from the subject samples and the limited availability of paired RNA samples of sufficient quality

prevented a more complete analysis of a greater number of genes from a larger number of subject biopsies.

Therefore, it is not possible to draw firm conclusions regarding the mechanism of action of CNTO 1275 based upon these results. Larger studies may provide further insights on potential connections of these observations to the pathology of psoriasis and the mechanism of action of CNTO 1275”.

d. Publication: Toichi et al., J. Immunol. (2006), 177 :4917-4926

An exploratory retrospective study with 18 patients with moderate to severe psoriasis treated with 0.1, 0.3, 1.0 or 5.0 mg/kg of anti-IL-12p40 monoclonal antibody is described in this publication. Histopathological changes, mRNA expression and immunohistochemistry of selected cytokines and chemokines in psoriasis patients were examined. Expression of IFN- γ and of chemokines such as IL-8, IFN- γ -inducible protein-10 and MCP-1 were significantly reduced at 2 weeks post-treatment. Interestingly, decreased TNF- α levels and infiltrating T cells were observed in high responders, but not in low responders. The levels of IL-12p40 and of IL-23p19 were also decreased in both responder groups. Baseline values of TNF- α have been suggested to have predictive value of therapeutic responsiveness.

4. QUESTION-BASED REVIEW

a. Are the technical aspects of the gene expression studies acceptable?

Based on the available details, the technical aspects appear to be acceptable. Some questions remain.

1. Whether any RNase inhibitor added to the biopsy sample before pulverizing it?
2. Were RIN numbers used in the QC of RNA using the Agilent bioanalyzer?
3. Why was 18S RNA used as an endogenous control in one study and GAPDH in the other studies?
4. If the PCR reactions were run in triplicate, was the data expressed as an average of all three or best two out of the three?

b. Are the findings of gene expression studies consistent across the studies?

As the Sponsor has mentioned, microarray data is definitely of exploratory nature. Thus, only TaqMan RT-PCR data will be considered for the review. Study CSR C0379T01 with 18 subjects treated with 4 different doses of CNTO 1275, showed a decrease in mRNAs for IFN γ , IL-12p40, IL-10, IL-8, TNF- α and IP-10 for all the doses examined at two weeks. It was reported in Study CSR C0379T02 that IL-12p40 mRNA levels were reduced after CNTO 1275 treatment (data not shown). In study CSR C0379T04, inconclusive results were obtained for IL-12/23 p40 mRNA levels. Based on the microarray

data, different targets were selected and a decrease in mRNA levels for SERPINB3, SERPINB4, GJB2 and IL1F9 were identified in the 90mg responder group. In brief, several exploratory biomarkers in the gene expression studies have been identified, but none have been confirmed.

- c. Is the sample size adequate for concluding that the expression of inflammatory cytokines and chemokines such as MCP-1, TNF- α , IP-10 and IL-8 is reduced in lesional skin biopsies?

The sample size in each dose group is very small and promising exploratory biomarkers have been identified in the studies. However, preliminary data indicates that the expression of mRNAs of inflammatory cytokines and chemokines such as MCP-1, TNF- α , IP-10 and IL-8 is reduced in lesional skin biopsies.

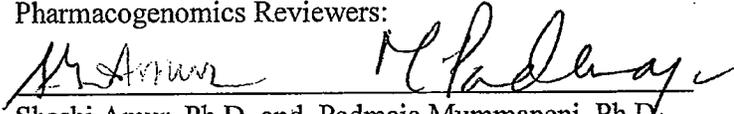
5. LABELING RECOMMENDATION

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Signatures:

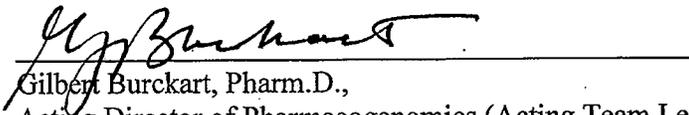
Pharmacogenomics Reviewers:



July 31st, 2008

Shashi Amur, Ph.D. and, Padmaja Mummaneni, Ph.D.
Pharmacogenomics Reviewers,
Office of Clinical Pharmacology

Pharmacogenomics Team Leader:



July 31st, 2008

Gilbert Burckart, Pharm.D.,
Acting Director of Pharmacogenomics (Acting Team Leader),
Office of Clinical Pharmacology

Nonclinical

CNTO 1275 binds the p40 protein subunit of primate as well as human IL-12 and IL-23. Toxicology studies with CNTO 1275 were performed in cynomolgus monkeys. The sponsor states in the 9 Apr 2007 IB “In toxicology and preclinical studies of CNTO 1275, no CNTO 1275-related cardiovascular toxicities or CNTO 1275-related ECG findings have been observed in safety studies in cynomolgus monkeys following IV doses up to 45 mg/kg/week for up to 1 month and following twice weekly SC doses up to 45 mg/kg for 6 months.”

CNTO 1275 binds to human IL-12 and IL-23 with high affinity *in vitro*; however, it did not bind to cardiac tissue in *in vitro* immunohistochemical investigations of cross-reactivity.

Clinical

As of 31 Dec 2006, 7 clinical studies of CNTO 1275 administration to 789 subjects (701 exposed) have been completed:

- C0743T11: a phase 1 PK study of a single 90 mg SC dose in 31 male healthy subjects
- C0379T01: an uncontrolled phase 1 study of single ascending IV doses of 0.09 – 4.5 mg/kg in 24 psoriasis patients
- C0379T02: a placebo controlled, blinded phase 1 study of single ascending SC doses of 0.27 – 2.7 mg/kg in 21 psoriasis patients
- C0379T03: a placebo controlled, blinded phase 1 study of single ascending SC doses of 0.27 – 2.7 mg/kg in 20 MS patients
- C0379T04: a placebo controlled, blinded phase 2 study of administering multiple doses of up to 90 mg SC weekly for four weeks to 318 patients with psoriasis
- C0743T06: a placebo controlled, blinded phase 2 study of administering multiple doses of up to 180 mg SC weekly for nineteen weeks to 249 patients with MS
- C0379T07: a placebo controlled, blinded phase 2 study of administering 90 mg SC or 4.5 mg/kg IV for four weeks to 131 patients with Crohn’s Disease

No deaths are reported in any completed clinical study of CNTO 1275. Three cardiac SAEs are reported, two myocardial infarctions and one heart failure.

Additionally, 2164 subjects have been randomized in four ongoing phase 2 and 3 studies:

- Two randomized, double-blind placebo-controlled phase 3 studies of 45 or 90 mg SC at 0 and 4 weeks and then starting at 16 weeks q12 weeks in 1996 psoriasis patients
- One phase 1 study in Japanese patients
- One ongoing phase 2 study in 143 psoriatic arthritis patients

In one of the ongoing phase 3 studies in psoriasis, a 33-year-old male subject who had had received two 90 mg doses of CNTO 1275 died suddenly cardiac death at Week 5 of the study. Autopsy revealed congestive cardiomyopathy.

Other serious cardiovascular AEs that have been reported include five MIs, one ventricular tachycardia, and one heart failure.

Current submission

“Centocor has additionally undertaken a comprehensive review of pre-clinical and Phase 1 and 2 clinical safety data. After reviewing the data, the following conclusions were made:

Preclinical research has demonstrated that CNTO 1275 binds to the p40 protein subunit that is common to both IL-12 and IL-23 with high affinity and specificity, that CNTO 1275

did not bind to human cardiac tissue, and no CNTO 1275-related adverse effects on blood pressure, heart rate, ECG recordings, or cardiac histopathology were observed in toxicology studies where cynomolgus monkeys were administered 45 mg/kg/week, a 45-fold excess, when compared with the highest equivalent dose intended to be administered to psoriasis patients.

The ECG evaluations that were incorporated into all Phase 1 studies and in a subset of subjects in the Phase 2 psoriasis study have been re-evaluated with particular emphasis on QT / QTc prolongation. Overall, no clinically significant observations or changes from baseline values were observed for heart rate, PR interval, QRS interval or QT / QTc. There were no individual QTc measurements that suggested QT prolongation. No QTcF values above 450 ms in men or above 470 ms in women after CNTO 1275 treatment were observed. No change from baseline QTcF greater than 60 ms was observed. There was also no consistent change in these parameters in terms of CNTO 1275 dose or time from treatment administration.

These data, in conjunction with the available preclinical data suggest that CNTO 1275 is very unlikely to have an effect on delaying cardiac repolarization. Centocor intends to continue monitoring ongoing and future clinical trials, including trials comprising Phase 3 development, for adverse events and safety signals. However, Centocor's current assessment is that the CNTO 1275 development program has adequately addressed ICH E14 and that additional QT/QTc assessment or study is not warranted."

Additionally, the sponsor submits outlines for nonclinical studies of NOMAC's effects on the hERG current in HEK-293 cells and on the ECG after administration to conscious female cynomolgus monkeys.

Finally, the sponsor submits a protocol outline for a phase 1 pharmacokinetic study of NOMAC-E2 after single and multiple doses. A secondary objective of this study is to explore the effect of a single dose of NOMAC-E2 on the QTc. The portion of the protocol designed to evaluate the QTC effect involves randomizing 25 females 4:1 to either a single dose of the therapeutic dose of NOMAC-E2 or placebo and then collecting ECG data over the next 24 hours without concomitant blood sampling for PK.

QT-IRT Comments for DDDP:

1. In our opinion, monoclonal antibodies do not need to be evaluated in a thorough clinical QT study because:
 - a. as large molecules, monoclonal antibodies cannot access the hERG pore via the intracellular side, which is the target site for most small-molecule QT-prolonging drugs; and
 - b. monoclonal antibodies can have off-target cardiac effects but QT prolongation has not been observed.
2. We recommend that routine ECG monitoring in clinical studies should be performed to capture any important effects. Centocor has incorporated ECG evaluation in their phase 1 and 2 studies and plans to continue ECG monitoring in phase 3 studies. The QT-IRT has not reviewed the ECG data collected in these studies.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderderpqt@fda.hhs.gov

Linked Applications

Sponsor Name

Drug Name

IND 9590

CENTOCOR INC

Human Monoclonal Antibody (CNTO 1275)
to Interleukin 12p40

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE E GARNETT
02/08/2008
Clinical Pharmacology Reviewer

NORMAN L STOCKBRIDGE
02/08/2008
Clinical Reviewer

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA**

NDA/BLA Number: STN # 125261/0 Applicant: Centocor Inc.

Stamp Date: 28th November, 2007

Drug Name: Ustekinumab (CNTO 1275) NDA/BLA Type: Original BLA Application

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

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X	The drug product used in the pivotal clinical trials is the same as the to-be-marketed drug product.
2	Has the applicant provided metabolism and drug-drug interaction information?	X		
Criteria for Assessing Quality of an NDA				
Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	X		Format used for this application is the eCTD
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			Not Applicable
Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		See clinical filing review for further details
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	X		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			Not Applicable
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			Not Applicable
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA**

General				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____ Yes _____

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

Not Applicable

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

None

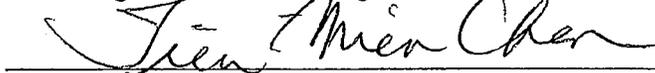
Abimbola Adebowale



01-07-08

Reviewing Clinical Pharmacologist

Date



01/10/08

Team Leader/Supervisor

Date