



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Dermatologic and Ophthalmic Drugs Advisory Committee
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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 IgG1 antibody directed against the p40 subunit of the IL-12 and IL-23 cytokines. The IL-12 and IL-23 cytokines are comprised of a shared p40 subunit and a subunit 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.

Ustekinumab is an immunosuppressant. The immunosuppression is of prolonged duration because of the product's long-half life of approximately three weeks.

The Committee is asked to provide specific advice and recommendations on the issues detailed below, including identification of informational gaps. Following discussion of the risk/benefit profile for this product, the Committee will be asked to provide recommendations on approval.

Specific Issues for Discussion:

1. Efficacy/Dosing:

To establish efficacy, the applicant conducted two adequate and well-controlled trials with a primary efficacy timepoint at 12 weeks (dosed at week 0 and 4). Additionally, maintenance of effect was evaluated through week 28 (dosed at week 16).

The applicant did not determine the optimal dosing regimen (dose, duration, frequency) prior to initiation of phase 3 trials, but studied two doses (45mg, 90mg). Efficacy was established for both doses, but heavier subjects had a higher success rate with the 90mg dose. As a result, the application includes multiple dosing scenarios.

The product is proposed for fixed dosing by two weight categories:

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

Analyses reveal a relationship between efficacy outcomes (PASI) and weight. For example, higher success rates are seen in heavier subjects dosed with 90 mg compared to

45 mg. Analyses also reveal a relationship between the pharmacokinetics of ustekinumab, efficacy outcomes and weight. Serum concentrations and efficacy outcomes appear to follow a continuum when body weight is considered, and these interrelations are not entirely reflected in the sponsor's proposed dosing by strict weight categories of ≤ 100 kg and >100 kg.

Based on AUC-PASI response rate analysis, weight-based dosing adjustments other than those proposed by the applicant have been explored and will be presented for the Committee's consideration.

The Committee is asked to discuss whether the applicant's and the alternative weight-based dosing paradigms and make a recommendation on which one should be approved, if any.

2. Carcinogenicity:

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

Language reflecting what is known about the carcinogenicity potential from the literature reports of animal studies would be proposed by the Agency for inclusion in the label, if a decision is made for approval. The Committee is asked to consider whether the proposal to include in the label the findings from animal studies, which indicate an increased carcinogenic risk with inhibition of IL-12/IL-23 expression, is adequate to communicate the potential increased carcinogenic risk from use of ustekinumab, or whether additional studies would be useful.

3. Long-term Safety:

a. The applicant has 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)

Ustekinumab blocks IL-12/IL-23, and as such may carry an increased risk for malignancy. Additionally, the prolonged period of immunosuppression could impact the risk of malignancy and other adverse events. The Committee is asked to discuss what number of subjects followed for what period would constitute a sufficient number of subjects followed for a sufficient duration to adequately inform the long-term safety of ustekinumab pre-approval, and whether products that increase the risk of malignancy might require more long-term safety data pre-approval than might be required for a product not known to carry such a risk.

b. The applicant has proposed a multi-center, prospective, longitudinal, 8-year, observational study (PSOLAR) of long-term safety and clinical outcomes in patients with all forms of psoriasis, who are candidates for systemic therapy and are at least 18 years of age. As currently proposed, PSOLAR may not be the best research design to study the long-term safety of ustekinumab or rare outcomes that might be associated with its use, such as malignancies. Limitations to the design include the limited absolute size, voluntary participation and issues of loss-to-follow-up. An alternative option could be a mandatory long-term registry where all individuals exposed to ustekinumab are included. Input from the Advisory Committee on the optimal approach would be useful.

4. Self-administration:

The safety and efficacy data collected during the development program regarding self-administration reflect such being done at the clinical site under medical supervision and not “real-world” use. Maintenance dosing is proposed for 12-week intervals, and the applicant proposes that subjects could self-administer these maintenance treatments. This would seemingly allow for intervals longer than three months between scheduled office visits, which could result in a delay in diagnosis and/or treatment of clinically-significant events that might impact the appropriateness of continuing treatment and maintaining the prolonged state of immunosuppression. The Committee is asked to discuss the clinical significance of allowing self-administration, which could preclude office visits, and evaluation of safety and efficacy outcomes, and adverse events for individual patients.

Ustekinumab—Mechanism of Action

Ustekinumab is a fully human IgG1 antibody directed against the p40 subunit of the IL-12 and IL-23 cytokines. The antibody was developed in a transgenic mouse strain in which the mouse immunoglobulin genes have been inactivated and replaced with the human immunoglobulin genes allowing the generation of fully human antibodies. Recombinant DNA technology was subsequently used to allow monoclonal antibody production by a well characterized cell line. Purification of the antibody is done using standard bio-processing technology.

The IL-12 and IL-23 cytokines are comprised of a shared p40 subunit and a subunit unique to each cytokine, p35 for IL-12 and p19 for IL-23. The receptors for IL-12 and IL-23 are comprised of a common receptor chain, IL-12 β 1, and a receptor chain unique to each cytokine (Kang and Kim, 2006). The binding of p40 by Ustekinumab disrupts the interaction of p40 to the shared receptor chain, IL-12 β 1, thus inhibiting signaling by both IL-12 and IL-23.

IL-12 and IL-23 are primarily produced by activated cells of the innate immune system, such as dendritic cells and macrophages. IL-12 is an inflammatory cytokine whose signaling results in the activation of NK and CD8+ T cells, the differentiation of CD4+ T cells into Th1 cells, and the production of IFN γ : activities that play a major role in tumor surveillance and host defense against infections (Kastelein, et al., 2007; Kang and Kim, 2006). A major role for IL-23 signaling is the induction of Th17 cell development (Laurence and O'Shea, 2007). There is growing evidence that Th17 cells, and the cytokines that they produce, are critical for both host defense mechanisms and the pathogenesis of multiple autoimmune diseases, such as psoriasis (Nickoloff, 2007; Ouyang et al., 2008; McGeachy and Cua, 2008).

The contribution of IL-12 and IL-23 to the psoriatic process is still evolving. Originally psoriasis was considered to be a Th1/ IL-12 driven disease, and this concept was supported by data such as those indicating p40 mRNA and IFN γ upregulation in psoriasis. However, an appreciation for the role of IL-23 in psoriasis has recently developed due to the recognition that it is also comprised of a p40 heterodimeric protein. The role of IL-23 as a mediator of the psoriatic inflammatory process is supported by a variety of data, including reports demonstrating; upregulation of the p19 subunit of IL-23, but not the p35 subunit of IL-12, in psoriasis plaques (Lee et al., 2004; Torti and Feldman, 2007); the association of Th17 cytokines with psoriasis (Fitch et al., 2007); and the recognition that IFN γ production can be driven by either IL-12 or IL-23 (Laurence and O'Shea, 2007; Wilson et al., 2007; Blauvelt, 2008; Sabat et al., 2007). Collectively, these data point to psoriasis as an IL-23/Th17 driven disease and therefore Ustekinumab's primary mechanism of action may be the inhibition of IL-23 signaling and down-modulation of Th17-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 the cytokine TNF α , an inflammatory cytokine produced during psoriasis. (Boker, A. et al, 2007, Boehncke et al 2006, Lowes et al 2007)

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Nonclinical Studies of Human Monoclonal Antibody Ustekinumab

Special toxicology: Tissue cross-reactivity studies showed that the cynomolgus monkey was the pharmacologically relevant toxicology species.

Pharmacokinetics/Toxicokinetics: Pharmacokinetic/toxicokinetic studies with ustekinumab have been conducted in monkeys. The mean $t_{1/2}$ values ranged from 2-3 weeks following multiple subcutaneous injection of ustekinumab in monkeys. However, low levels of ustekinumab were detected in some control (PBS-treated) monkeys.

General toxicology: Ustekinumab has been tested in cynomolgus monkeys by intravenous or subcutaneous administration at doses up to 45 mg/kg twice weekly for up to 6 months. Some safety pharmacology endpoints have been examined in monkeys. No significant adverse effects were noted in these studies, except that in the 26-week subcutaneous study, one out of eight male monkeys given 50 mg/kg exhibited signs of bacterial enteritis during Week 26 and a possible contribution of ustekinumab to this infection could not be excluded.

Genetic toxicology: No genetic toxicology studies have been conducted with ustekinumab.

Carcinogenicity: Nonclinical carcinogenicity studies have not been conducted with ustekinumab. No tumors or histopathological evidence of pre-neoplastic changes were observed in organs or tissues examined following subcutaneous administration of ustekinumab to monkeys at dose levels up to 45 mg/kg twice weekly for 6 months followed by a 3-month post-dose observation period. The sponsor proposed to monitor malignancy in psoriasis patients administered ustekinumab as a part of a comprehensive Risk Management Plan for ustekinumab.

The risk of malignancy in patients is a safety concern for immunosuppressive drugs. Ustekinumab, an antibody to IL-12/IL-23p40, is a selective immunosuppressant. It presumably inhibits the bioactivity of human IL-12 and IL-23 by preventing these cytokines from binding to their IL-12R β 1 receptor protein expressed on the surface of immune cells, which further prevents IL-12 and IL-23 contributions to NK cell activation and CD4+ T cell differentiation and activation. Ustekinumab is believed to interrupt signaling and cytokine cascades that are central to psoriasis pathology. Since psoriasis is a chronic disease, psoriasis patients may be under treatment for long periods of time. Long term use of ustekinumab may lead to increased risk of tumor development in psoriasis patients, particularly in those who have been exposed to other therapies which could increase the risk of tumor development, such as UVB, photodynamic therapy, and other immunosuppressive agents. Although published literature (Fieschi and Casanova, 2003) reported an observation that 73 subjects with genetic deficiencies in IL-12 signaling had not developed cancer, the information available on these subjects is not sufficient to determine whether the subjects have a different cancer risk than the general population. The number of subjects is relatively small and many of the subjects appear to be very young. It is not clear that these subjects were followed for a sufficient duration,

given the long latency of malignancy development. In addition, the fact that these subjects were susceptible to infections, presumably due to immunosuppression, may indicate a potential for increased cancer risk.

Ustekinumab can not be tested in a traditional 2-year rodent study to evaluate its carcinogenic potential, due to its species specific binding to humans and non-human primates. A mouse carcinogenicity study with an analogous antibody to mouse IL-12 may be an approach for carcinogenicity risk evaluation. Available scientific literature on animal studies suggests a potential malignancy hazard is associated with IL-12/IL-23p40 antagonism. IL-12 has been shown to play a critical role in tumor surveillance and host defense in rodents. Recent publications further demonstrated the association between IL-12 deficiency and the susceptibility to UV-induced skin tumors in mice.

Published studies showed that administration of murine IL-12 exerted an anti-tumor effect in mice, which was associated with enhanced anti-tumor activities of T cells and NK cells, induction of IFN- γ production and other cytokines induced-by IL-12, and potential secondary anti-angiogenic activities. In mice, intraperitoneal injection of murine IL-12 five times per week for 3 weeks reduced experimental pulmonary metastases of B16F10 melanoma cells, inhibited subcutaneous growth of established melanoma, reticular, and renal cell carcinomas, and increased survival time of tumor bearing mice in these models (Brunda et al, 1993). Sixteen weekly injections of IL-12 blocked carcinogenic progression in a mouse HER-2/neu oncogene-dependent mammary carcinogenesis model with established atypical hyperplastic mammary glands (Cifaldi et al, 2001). Intraperitoneal injection of murine IL-12 five days a week with an injection schedule of 3 weeks on and 1 week off for 18 weeks delayed tumor appearance and reduced tumor incidence in mice administered 3-methyl-cholanthrene (MCA) in a mouse MCA tumor promotion model (Noguchi et al., 1996). In addition, modest anti-tumor activity was noted in clinical trials for human IL-12 at doses which were over 10-fold lower than those tested in mice (Columbo and Trinchieri, 2002).

Data from IL-12/IL-23 knockout (KO) mice and data from studies in which IL-12/IL-23 activity is inhibited using neutralizing antibodies provide further evidence that IL-12/IL-23 contributes to endogenous host defense to neoplasia. Compared to the wild-type mice, IL-12/IL-23p40 KO mice developed UV-induced tumors earlier and more frequently, and tumors generated in IL-12/IL-23p40 knockout mice grew faster in vivo and had greater intrinsic invasive potential (Maeda et al, 2006). Similarly, the development of UV-induced tumors was more rapid and the tumor multiplicity and tumor size were significantly greater in IL-12p35 KO mice than the wild-type mice; the incidence of malignant transformation of UVB-induced papillomas to carcinomas was higher in IL-12p35 KO mice in terms of carcinoma incidence; UVB-induced DNA damage in the form of cyclobutane pyrimidine dimers was removed or repaired more rapidly in the wild-type mice than the IL-12p35 KO mice (Meeran et al, 2006). In contrast, one published paper (Langowski et al, 2006) showed that IL-12/23p40 KO mice were resistant to 9,10-dimethyl-1,2-benzanthracene (DMBA)-induced papillomas, although IL-12p35 KO mice showed earlier appearance and developed significantly increased numbers of papillomas induced by DMBA, compared to the wild-type mice. This paper

further suggested that “Genetic deletion or antibody-mediated elimination of IL-23 leads to increased infiltration of cytotoxic T cells into the transformed tissue, rendering a protective effect against chemically induced carcinogenesis.” However, a dramatically increased tumor incidence was seen in the IL-12p35 or IL-12/IL-23p40 KO mice, compared to the wild-type or IL-23p19 KO mice, after the mice were challenged intradermally with PDV squamous carcinoma cells (Langowski et al, 2006). Furthermore, mice treated with a neutralizing antibody to mouse IL-12/IL-23p40 to deplete both IL-12 and IL-23 had a significantly increased tumor incidence and developed larger, faster-growing tumors after challenge with PDV squamous carcinoma cells; treatment with anti-IL-12/IL-23p40 antibody also led to a marked increase of tumor growth and an increase of metastasis formation in mice bearing tumors formed by EP2 breast cancer cells (Langowski et al, 2006). Consistently, in rats bearing spontaneously regressing AK-5 rat histiocytoma cells, treatment with anti-IL-12 antibody caused the tumor size to be much larger and the animal life span was shorter, compared to the control animals (Rao et al, 1997). Although results from one literature paper suggested that “neutralizing antibodies to IL-12 did not inhibit antitumor efficacy of low dose melphalan in BALB/c mice bearing large MOPC-315 plasmacytoma burden” (Gorelick and Mokyr, 1995), which may be due to that anti-IL-12 antibody and melphalan work on different pathways, this reviewer believes that additional studies are needed to understand the role(s) of anti-IL-12 antibody on this observation.

In summary, based on a weight of evidence approach, published literature suggests that a potential malignancy hazard is associated with antagonism of IL-12/IL-23p40 in rodents. At this time, it appears that another 2-year carcinogenicity study with IL-12/IL23p40-depleted mice will not be very informative. Adequate labeling on animal data from literature and post-marketing patient monitoring of malignancy may be sufficient at this time.

Reproductive toxicology: A male fertility study, two embryo-fetal development toxicity studies, and an embryo-fetal development and pre- and postnatal development toxicity study have been conducted in cynomolgus monkeys at doses up to 45 mg/kg ustekinumab via subcutaneous or intravenous administration. A female fertility study was conducted in mice using an analogous IL-12/IL23 p40 antibody. No significant adverse effects were noted in these studies.

References:

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Efficacy of Ustekinumab in the Treatment of Psoriasis

Introduction

The efficacy of subcutaneous injections of ustekinumab 45 mg and 90 mg in the treatment of chronic plaque psoriasis was evaluated in two Phase 3 studies, PHOENIX 1 and PHOENIX 2. 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. PHOENIX 1 enrolled 766 subjects and PHOENIX 2 enrolled 1230 subjects. At the beginning of the study, 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. The applicant submitted data from PHOENIX 1 through Week 52 and from PHOENIX 2 through Week 28.

The applicant has proposed a recommended dosing schedule of injections at Week 0 and 4 and then every 12 weeks (Weeks 16, 28, 40, etc.). The applicant has proposed that patients ≤ 100 kg should receive 45 mg and that patients > 100 kg should receive 90 mg at each dosing timepoint.

Phase 3 Study Design – PHOENIX 1 and PHOENIX 2

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

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 database for PHOENIX 2 includes results through Week 28 (final injection at Week 16). The database for PHOENIX 1 includes results through Week 52 with a variable number of injections. In PHOENIX 1, 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).

Efficacy Endpoints and Primary Efficacy Evaluation

The primary efficacy timepoint was Week 12. The primary efficacy endpoint was PASI 75 ($\geq 75\%$ 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 (after adjusting for multiplicity) for PASI 75 response and PGA success at Week 12 in both studies ($p < 0.001$). See Table 1.

Table 1 – Efficacy Results at Week 12

	Ustekinumab 45 mg	Ustekinumab 90 mg	Placebo
PHOENIX 1	N=255	N=256	N=255
PASI 75 Responders	171 (67%)	170 (66%)	8 (3%)
PGA Cleared or Minimal	154 (60%)	158 (62%)	10 (4%)
PHOENIX 2	N=409	N=411	N=410
PASI 75 Responders	273 (67%)	311 (76%)	15 (4%)
PGA Cleared or Minimal	278 (68%)	302 (73%)	20 (5%)

All p-values for 45 mg vs. placebo and 90 mg vs. placebo are < 0.001

Maintenance of Effect

The studies were designed to obtain efficacy results for the initial treatment cycle (Weeks 0 and 4) and one 12-week maintenance dose (Week 16) through Week 28 for all subjects originally randomized to active treatment. The PASI 75 response rates over time through Week 28 are presented in Figure 1 and Figure 2 for the two studies. The proportion of subjects who respond at the end of the initial treatment cycle (Week 16) is maintained through the first maintenance period (through Week 28) for both the 45 mg and 90 mg dose groups.

The information on 12-week maintenance therapy beyond Week 28 is limited. The database for PHOENIX 2 was locked at Week 28, and this study does not provide any additional information on repeat dosing of ustekinumab. In the other study, PHOENIX 1, only subjects who responded to their randomized dose and were able to maintain response for 12 weeks after their last dose were permitted to continue every 12 week

dosing. Of the subjects originally randomized to active treatment, approximately 70% continued every 12 week dosing at Week 28, and approximately 30% continued every 12 week dosing at Week 40. See Table 2 for details. Approximately half of the subjects who were responding to every 12 week dosing at Week 40 were randomized to withdraw treatment rather than continue the every 12 week dosing.

Figure 1 – PASI 75 Response Rates over Time (PHOENIX 1)

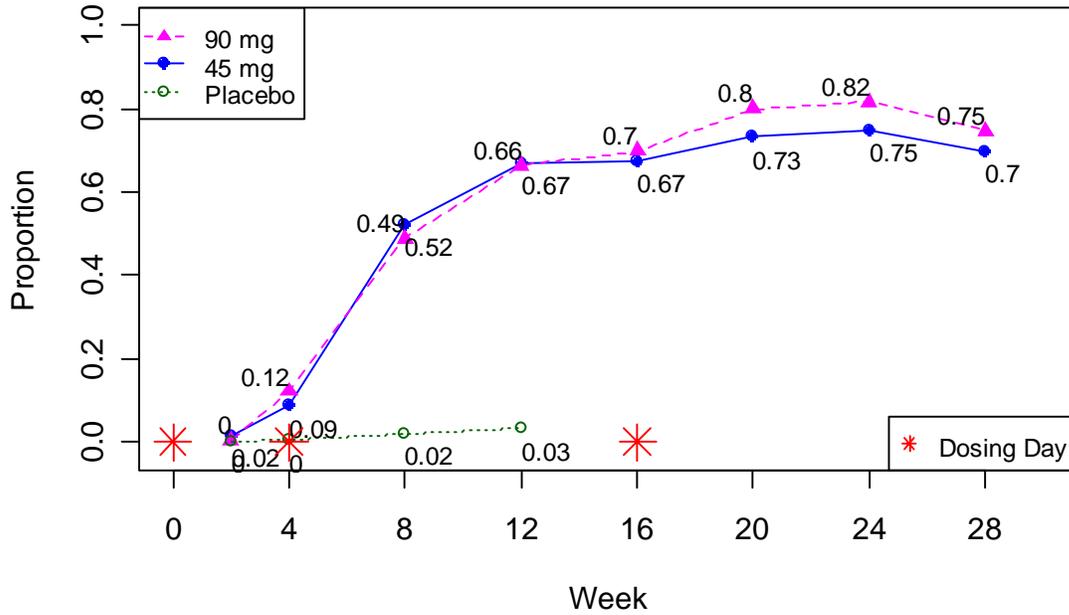


Figure 2 – PASI 75 Response Rates over Time (PHOENIX 2)

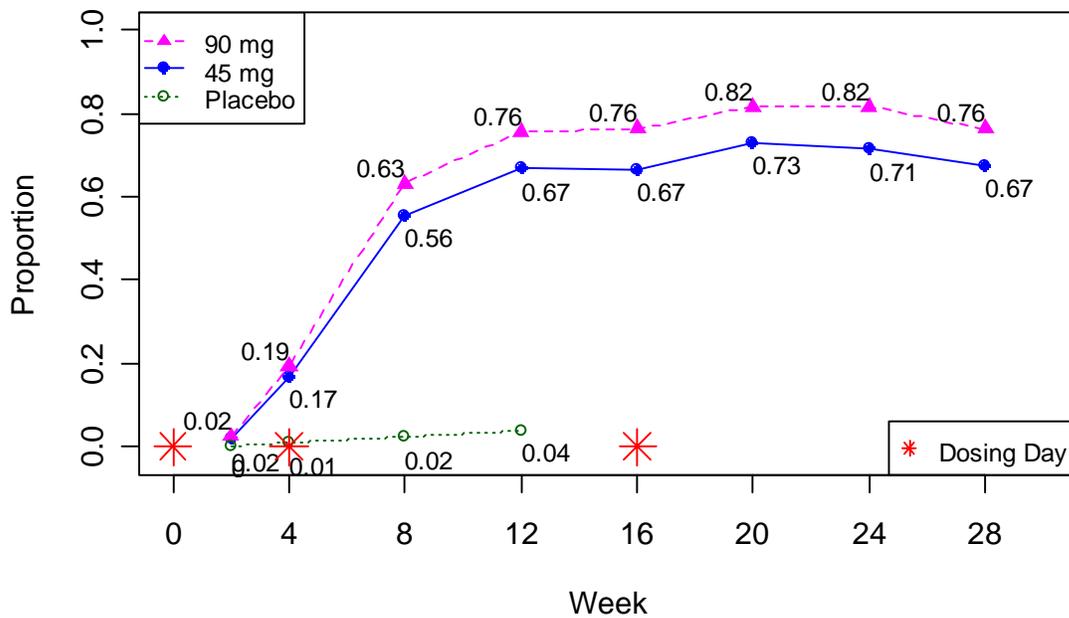


Table 2 – Number of Subjects Receiving 12-Week Maintenance Doses among Subjects Originally Randomized to Active Treatment (PHOENIX 1)

	Ustekinumab 45 mg N=255	Ustekinumab 90 mg N=256
Subjects originally randomized to receive doses at Weeks 0, 4, and 16 (initial cycle and 1 st maintenance dose)	255 (100%)	256 (100%)
Responders at Week 28 assigned to receive dose at Week 28 (2 nd maintenance dose)	177 (69%)	187 (73%)
Responders at Weeks 28 and 40 randomized to receive dose at Week 40 (3 rd maintenance dose)*	77 (30%)	85 (33%)

*Subjects responding at Weeks 28 and 40 were randomized 1:1 to receive a dose at Week 40 or withdraw treatment. Among subjects responding at Weeks 28 and 40 to 12-week dosing, 73 (29%) of 45 mg subjects and 87 (34%) of 90 mg subjects were randomized to withdraw treatment.

Continuing every 12 week dosing from Week 28 on was contingent on being a responder at the end of the previous dosing interval. Among subjects who previously were able to respond to treatment and maintain response for at least 12 weeks, taking an additional maintenance dose will allow approximately 86% of subjects taking 45 mg and 92% of subjects taking 90 mg to maintain response for at least another 12 weeks. See Table 3. The only information about intervals longer than 12 weeks comes from the subjects randomized to withdrawal at Week 40. Again, these were all subjects who previously responded to treatment and were able maintain response for at least 12 weeks. Among this group of subjects, approximately 64% maintained response for an additional 12 weeks (24 weeks from their last dose). Thus, some subjects who respond to treatment may be able to maintain response for more than 12 weeks after a treatment, though other subjects benefited from continuing 12-week dosing (87% - 91% of Week 40 responders who got a dose at Week 40 maintained a response at Week 52 compared to 63% - 64% of Week 40 responders who did not get a dose at Week 40). The applicant has not otherwise evaluated periods longer than 12 weeks between maintenance doses or evaluated other maintenances strategies such as reducing dose concentrations.

Table 3 – Percentage of PASI 75 Responders at Key Timepoints

	Ustekinumab 45 mg N=255	Ustekinumab 90 mg N=256
Proportion of <i>Originally Randomized Subjects</i> who were Responders at Week 28 (after doses at Week 0, 4, 16)	70% (178/255)	75% (191/256)
Proportion of <i>Week 28 Responders</i> who were also Responders at Week 40 (after additional dose at Week 28)	85% (151/177)	93% (173/187)
Proportion of <i>Week 28 and Week 40 Responders</i> who were also Responders at Week 52 (after being	87% (67/77)	91% (77/85)

randomized to an additional dose at Week 40)		
Proportion of <i>Week 28 and Week 40 Responders</i> who were also Responders at Week 52 (after being randomized to withdrawal at Week 40)	64% (47/73)	63% (55/87)

Response by Weight Subgroup

The Applicant has proposed dosing patients ≤ 100 kg with 45 mg and patients > 100 kg with 90 mg. Randomization was stratified on weight (≤ 90 kg vs. > 90 kg) and subgroup analyses indicate that weight may be a factor in selecting the most optimal dose. Although the study was designed to allow assessment of weight-based subgroups, the study was designed to demonstrate the efficacy of either or both dose groups in the whole study population. Because efficacy was demonstrated for both dose groups in the whole population, post hoc exploration of weight-based dose refinements between these two doses are acceptable.

The following figures (Figure 3 and Figure 4) present smoothed estimates of PASI 75 response rates by weight at Week 12 and Week 28. These plots demonstrate that the success rates decrease as weight increases, and that the 90 mg dose does tend to have higher success rates than the 45 mg dose in the higher weight subjects.

Figure 3 – PASI 75 Response Rates at Week 12 by Weight

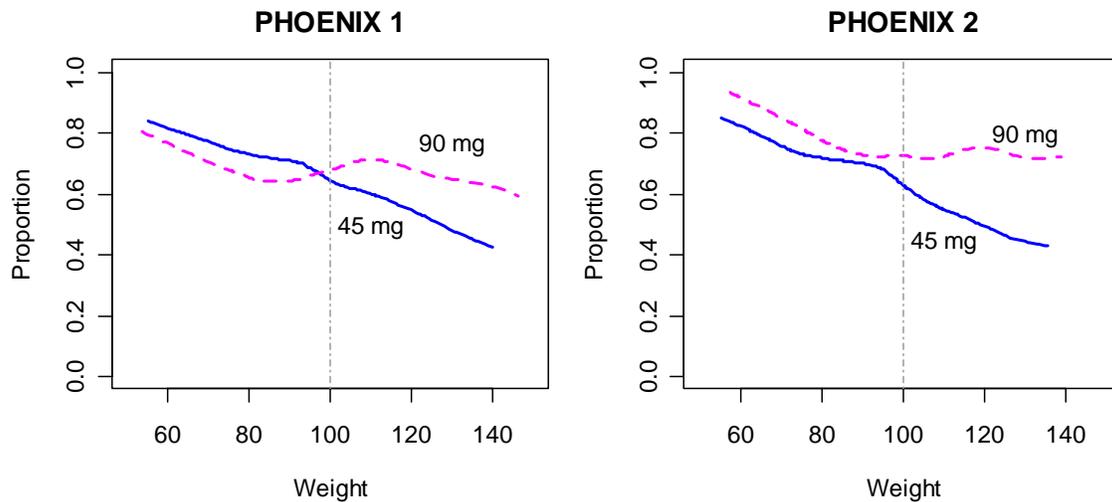
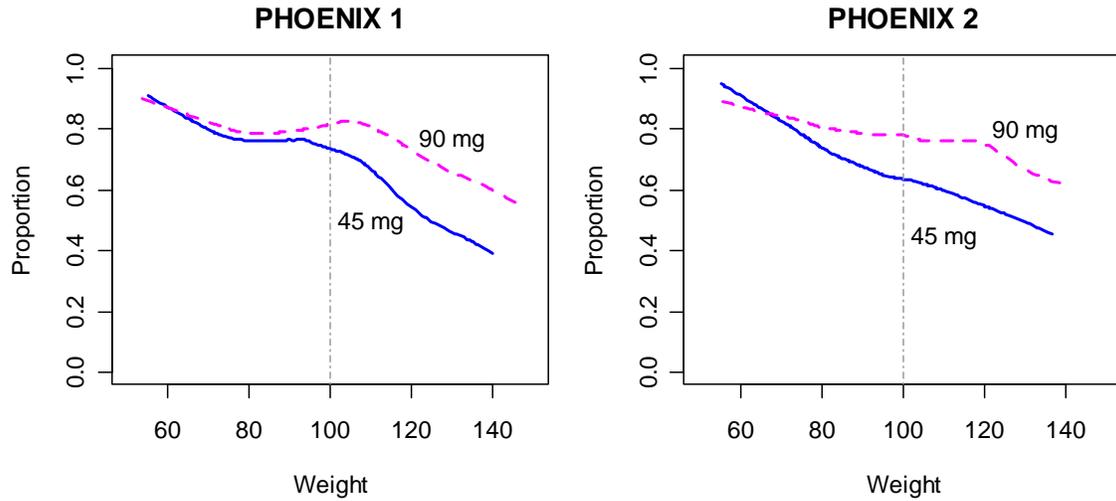


Figure 4 - PASI 75 Response Rates at Week 28 by Weight



In summary, the studies have demonstrated that both the 45 mg dose and the 90 mg dose are efficacious. The applicability of recommendations based on results from data-driven exploratory analyses from a study to a broader patient population depend on the level of theoretical justification for the results, as arbitrary subgroup differences can occur in studies by chance.

Summary of the Clinical Pharmacology and Biopharmaceutics Findings

Introduction:

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 (HS). C0379T01 and C0379T02 were Phase 1 psoriasis studies evaluating single intravenous (IV) and subcutaneous (SC) administration, respectively, of weight adjusted doses of CNTO1275 (ranging from 0.09 mg/kg – 4.5 mg/kg). C0379T04 was a Phase 2 psoriasis study evaluating 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) 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. The single-dose pharmacokinetic (PK) study (C0743T11) conducted in healthy subjects evaluated a single dose of the highest proposed dose strength (90 mg SC) of the liquid in vial formulation intended for the commercial product.

The pharmacokinetic (PK) assessments included intense and/or sparse blood sampling for the analysis of serum CNTO 1275 concentrations. The PK of CNTO1275 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). Traditional non-compartmental method was used to analyze the PK data in these early Phase 1 and 2 studies. 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.

In the analysis of exposure-response relationship and pharmacometric dosing recommendation, data from the two Phase 3 studies (C0743T08 and C0743T09) conducted in subjects with moderate to severe plaque-type psoriasis were used. The PASI response rate of CNTO 1275 was established using a total of 1331 (664 [45 mg] and 667 [90 mg]) CNTO 1275 treated and 665 placebo treated subjects (see statistical analyses for details). The results were further supported by week 28 data and placebo crossover groups. Dose response for psoriasis area and severity index (PASI) response rate was generally observed in all treatment groups with approximately 10% difference in PASI75 response between 45 and 90 mg dose groups. Data from Phase 1 and 2 studies (C0379T01, C0379T02, and C0379T04) further supported dose-dependent improvement in PASI with a greater degree of PASI improvement and duration of response seen in the higher dose groups.

CNTO 1275 exposure-PASI response rate analysis was used to answer ‘what is the optimal starting dose of CNTO 1275?’ The key findings of the analysis were:

1. Psoriasis improvement is dependent on serum CNTO 1275 exposures

2. At a given dose, serum concentrations (and area under the concentration-time curve [AUC]) in heavier subjects (117 kg body weight) are 50% compared to those in lighter subjects (68 kg).
3. Due to PK differences, the efficacy (PASI75) response rate in heavier subject is lower than the rate in lighter subjects.
4. 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 CNTO 1275:

Absorption:

In subjects with psoriasis (C0379T02 and C0379T04), the median time to achieve maximum concentration (T_{max}) occurred between 7 to 14 days after a single SC administration of approximately 24 mg to 240 mg doses (based on an assumed body weight of 90 kg in psoriasis patients). In healthy subjects (C0743T11), the median T_{max} occurred approximately 8.5 days after a single 90 mg SC administration. 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% following a single SC administration.

Distribution:

The median values of apparent volume of distribution at the terminal phase (V_z/F) following a single SC administration were approximately 79 to 161 mL/kg in psoriasis subjects (C0379T02 and C0379T04) and 86 mL/kg in healthy subjects (C0743T11).

Metabolism and Elimination:

The exact metabolic pathway for CNTO 1275 has not been characterized. In psoriasis subjects, the median terminal half-life (t_{1/2}) after a single SC administration (C0379T02 and C0379T04) was approximately 15 to 32 days. The median t_{1/2} after multiple SC administrations (C0379T04) was approximately 21 to 30 days. In healthy subjects, the median t_{1/2} obtained after a single 90 mg dose administration (C743T11) was approximately 20 days.

The median values of the apparent total systemic clearance (CL/F) following a single SC administration ranged from approximately 2.7 to 5.3 mL/day/kg in psoriasis patients (C0379T02 and C0379T04). The median CL/F following a single SC administration was 3.0 mL/day/kg in healthy subjects (C0743T11).

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 after a single SC administration at doses ranging from 0.27 to 2.7 mg/kg (approximately 24 mg to 240 mg, C0379T02) 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).

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 than the 45 mg dose group, with differences between the two groups showing dose proportionality. Steady state was achieved by Week 28 for all treatments. The median steady-state trough serum concentrations at Week 28 in study C0743T08 and C0743T09 was 0.21 and 0.26 $\mu\text{g/mL}$, respectively (45 mg every 12 weeks), and 0.47 and 0.49 $\mu\text{g/mL}$ 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.

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 \leq 100 kg.

Exposure-Response Analysis and Alternative Dosing Recommendation:

Key question: What is the optimal starting dose of CNTO 1275?

Psoriasis improvement (PASI response) is dependent on serum CNTO 1275 exposures. Subjects with higher median serum concentrations of CNTO 1275 generally had greater clinical responses, as measured by PASI response, than subjects with lower median serum concentrations of CNTO 1275 (Figure 5). For example, the PASI75 response rate at week 12 in 135 subjects that had undetectable serum CNTO 1275 concentrations was 37% as measured by PASI75. The response rate increased to 75% in subjects with median concentrations \geq 0.9 $\mu\text{g/mL}$.

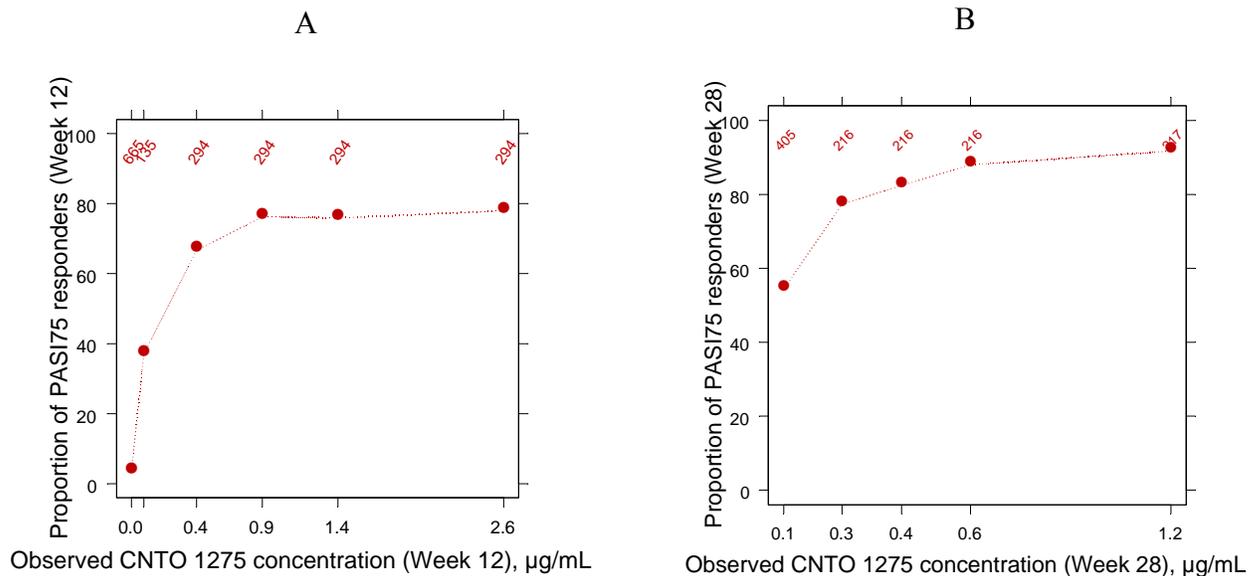


Figure 5: Relationship between serum CNTO 1275 concentration and proportion of PASI75 responders at week 12 (Panel A) and week 28 (Panel B). Placebo treated subjects and subjects with undetectable CNTO 1275 concentrations were plotted at

~0.1 µg/mL (0.085 µg/mL; 50% of lower limit of quantification), 0 µg/mL, respectively. Subjects with missing pharmacokinetic data at a given visit were ignored. The numbers corresponding to each quantile represent # of subjects.

The results were consistent across treatment groups (placebo crossover group at week 28- not shown), various time points (CNTO 1275 treated groups at Week 28; Figure 5, Panel B) and endpoints (PGA cleared- not shown) throughout both studies.

Due to PK differences, the (PASI75) response rate in heavier subjects is lower than response rate in lighter subjects (especially 45 mg)

The impact of weight on CNTO 1275 pharmacokinetics and PASI response rate was evaluated using observed serum CNTO 1275 concentrations and by PASI 75 response at Weeks 12 and 28, respectively, and analyzed by weight quartiles. There was a consistent impact of weight on pharmacokinetics and thereby PASI 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). Similarly, the response rate in the 45 mg group was impacted more (80% vs. 50%) between the highest and lowest weight quartiles. There was a minimal impact of weight on PASI response rate in the 90 mg group at both Weeks 12 and 28, because reasonable CNTO 1275 levels were achieved (Figure 6).

Therefore, the PK and PASI 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.).

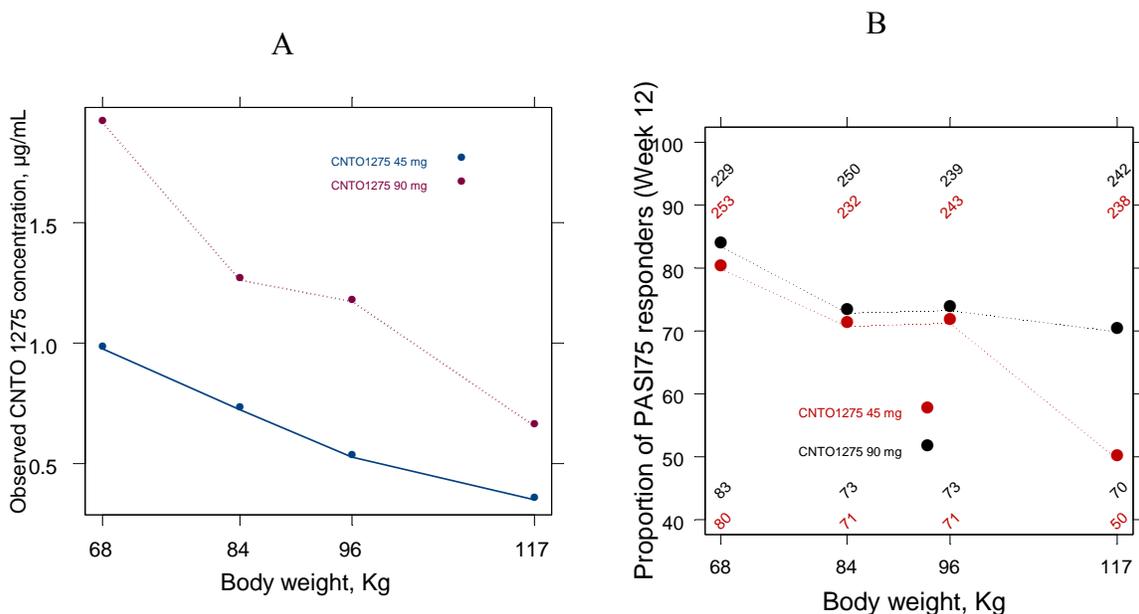


Figure 6: Panel A: Relationship between geometric mean CNTO 1275 concentration at week 12 and body weight quartiles. Subjects with undetectable CNTO 1275 concentrations were given a value of 0.085 µg/mL (50% of lower limit of

quantification); CNTO 1275 AUCs would follow a similar pattern. Panel B: Relationship between proportion of PASI75 responders at week 12 and body weight quantiles. The numbers represent response rate (bottom) and # of subjects (top) at each quantile.

Evaluation of alternate dosing regimens

Given the dependency of CNTO 1275 exposures on body weight, and PASI75 response rates on CNTO 1275 exposure, dose adjustment based on body weight would be necessary to maintain efficacy. The population pharmacokinetic model developed by the applicant was used to derive AUCs in individual subjects. A CNTO 1275 AUC (Week 0-12) – response (proportion of PASI75 responders) model was developed to evaluate alternate dosing regimen to gain insight into dosing regimens to maximize PASI response rate. The AUC-PASI response rate model described the data fairly well as shown in Figure 7. CNTO 1275 AUC was the most important predictor of PASI75.

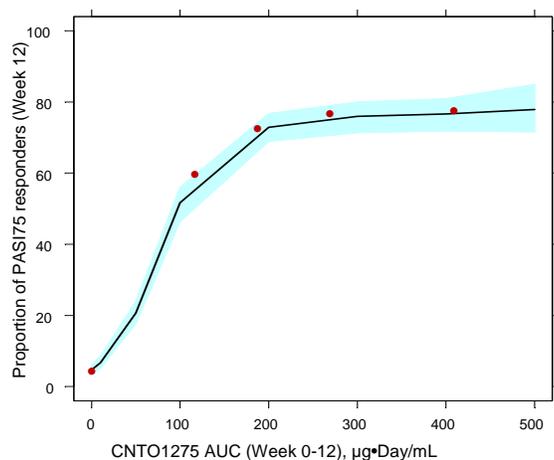


Figure 7: Relationship between CNTO 1275 AUC (Week 0-12) and proportion of PASI75 responders. The line represents median prediction and shaded area represents 95% CI of likelihood (PASI75) at week 12 as a function of CNTO 1275 AUC. The dots represent observed quantiles.

The AUC-PASI 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 PASI 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 4). The key findings from exploring alternative dosing strategy were:

- PASI response rate can be further maximized by weight based adjustment.
 - Administration of CNTO 1275 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 CNTO 1275 based on 3 step body weight cut offs (<60, ≥60-<90 and ≥90 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 PASI 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.
- Each of the body weight based adjustments explored here offer improved control over pharmacokinetics in the order listed in Table 4.

Finally, each of the dosing strategies explored here offer different advantages and disadvantages. The choice of dosing strategy should be based on benefit-risk assessment of CNTO 1275. Due to the limitations in the dataset, safety endpoints were not included

as a factor in establishing the dosing cut-offs as the relationship between pk and safety is not established with the required precision.

Table 4: 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 quantiles)				
		Overall	68 kg	84 kg	96 kg	117 kg
One dose for all	45	65	77	70	63	52
One dose for all	90	75	81	76	73	69
Weight based dosing adjustments						
Two-Step	<100kg: 45mg ≥100kg: 90mg	70	77	70	66	69
Three-Step	<60kg: 45mg ≥60-<90kg: (0.75mL) 67.5mg ≥90kg: 90mg	74	79	75	73	69
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	80	76	73	69
Semi-Continuous	<45kg: 45mg 45-90kg: 1mg/kg ≥90kg: 90mg	75	80	76	73	69

While the applicant’s proposed 2 step dosing regimen is sufficient to produce a therapeutic response in most subjects, there are subjects at each end of the dosing spectrum that are underserved. Adjusting the break points achieves some improvement, and the addition of an additional third grouping (the three step approach) appears to offer the benefit of improved efficacy outcomes to more patients with only a minor increase in dosing complexity. While the five step and semi-continuous approaches do offer a further improvement in overall efficacy, it is an increase limited only to 1 grouping

(68kg) based on the current model. Both of these approaches may also be more cumbersome in practice and could potentially result in a worse therapeutic outcome due to their complexity. The ease of dose calculation and dosing guidance should be part of the dosing considerations.

Pharmacodynamics:

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=38) 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 %).

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 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 %)

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 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.

Immunogenicity:

In the Phase 3 studies, the incidence of antibodies to CNTO was 5.1 % (38 out of 743 subjects) in C0743T08 through week 52 and 2.8 % (33 out of 1198 subjects) in C0743T09 through week 24. Subjects who were positive for antibodies to CNTO 1275 generally had lower median serum concentrations of CNTO 1275 than those subjects who were negative for antibodies to CNTO 1275. However, these results should be interpreted with caution due to the limitations of the assay method. The presence of CNTO 1275 in serum may interfere with the detection of antibodies to CNTO 1275 and thereby confound the interpretation of the immunogenicity analyses.

Safety

Safety Database

The applicant's product, ustekinumab, is an immunosuppressant. Risks from immunosuppressive therapy include an increased risk of infections and an increased risk of malignancies. It is possible that the risk of malignancy could be higher with ustekinumab relative to other immunosuppressants because ustekinumab binds IL-12, and IL-12 has been shown to play a role in tumor surveillance in animal models (see "Nonclinical Studies of Human Monoclonal Antibody Ustekinumab"). Additionally, ustekinumab has a long half-life, making for prolonged immunosuppression. This prolonged immunosuppression might also impact the risk of malignancy (as well as other adverse events associated with immunosuppression).

For a product intended for the long-term treatment of a non-life-threatening condition, regulatory guidelines describe that usually 300 to 600 subjects exposed for six months to dosage levels intended for clinical use "should be adequate to characterize the pattern of (adverse drug events) over time," and 100 subjects exposed at dosage levels intended for clinical use for a minimum of one year is acceptable for inclusion in the safety database (ICH-E1A: "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions"). However, the guidelines also state that larger safety databases may be needed to make risk/benefit decisions in certain situations.

In the applicant's Biological License Application (BLA), 1,602 subjects were considered to have been exposed to ustekinumab at doses intended for clinical use for at least six months (combined total for 45 mg and 90 mg), and 362 subjects were considered to have been exposed to ustekinumab for at least one year. Additional exposure data from the ongoing Phase 3 trials were submitted approximately four months subsequent to the original submission of the BLA. These data were for an additional 368 subjects with at least six months exposure to ustekinumab, an additional 923 subjects with at least one year of exposure and 373 subjects with at least 18 months of exposure. These additional data make the total reported exposed to ustekinumab at doses intended for clinical use to 1,970 for at least six months, 1,285 exposed for at least one year, and 373 exposed for at least 18 months.

The applicant's safety database integrated three studies, each with a follow-up period of different duration. The BLA included analyses to account for the different durations of follow-up (analyses by hundred subject years). The placebo period was the shortest duration of all the treatment periods. The following are a strict reporting of events and are not presented to convey a comparative analyses of occurrence of malignancies between treatment groups. Event reports of malignancies in the original BLA submission (i.e. prior to the additional data submitted four-months subsequent to the original submission) for subjects treated with ustekinumab included 21 non-melanoma skin cancers in 14 subjects, two reports of prostate cancer, and one report each of malignant kidney tumor, thyroid cancer and breast cancer. Event reports of malignancies in placebo

subjects were basal cell carcinoma and hepatic cancer. No lymphoproliferative malignancies were reported.

Because of the long latency period for malignancies, there is a question whether products that increase the risk might require more long-term safety data pre-approval than might be required for a product not known to carry such a risk. For the applicant's product, ustekinumab, it is unclear what amount of long-term safety data should be available for consideration in the pre-approval risk-benefit analyses and what amount could be submitted post-approval. It is not clear what number of subjects followed for what period would constitute a sufficient number of subjects followed for a sufficient duration to adequately inform the long-term safety of ustekinumab pre-approval. There is a question whether a larger number of subjects, followed for longer periods might better inform the long-term safety of use of ustekinumab.

Self-Administration

The applicant has proposed that select patients be offered the option of self-administration of ustekinumab in the maintenance phase of treatment. The intent of self-administration would seemingly be to permit use of ustekinumab outside of the clinical setting. It is not clear that the data presented adequately support this proposal. The broader safety concerns, however, do not relate to self-administration of subcutaneous injections, but relate to the product itself. It is not clear that ustekinumab, which induces prolonged immunosuppression, is appropriate for administration without benefit of medical evaluation prior to dosing.

The development program included some assessment of self administration; however, the protocols describe that subjects were to self-inject at the study site, under supervision of medical personnel. Therefore, safety and efficacy data collected from self-administration of ustekinumab reflect such being done under medically-supervised, clinical-trial conditions and not from real-world use. It is not clear that, for example, the adverse event profile generated from the product being self-administered under medical supervision would be reflective of the adverse event profile that might arise from self-administration outside of a controlled environment. It is possible too that patients would not become adept at self-injection procedures given the length of the intervals between treatments.

The long half-life of ustekinumab permits infrequent maintenance dosing. The long half-life also induces prolonged immunosuppression. As maintenance dosing is proposed at three-month intervals, administration by healthcare professionals would require in-office visits every three months. Self-administration, e.g. at home, could potentially result in far longer intervals between scheduled office visits, as patients would not need to present for treatments every three months. This could result in a delay in diagnosis and/or treatment of clinically-significant events that might arise during the course of (or as a function of) treatment.

Given the duration of immunosuppression, the risk-benefit equation and patient well-being may support assessment by a medical professional prior to re-treatment with a product that would sustain the immunosuppression. A minimum of four office visits a year for a determination that there is no change in health status that necessitates medical intervention and/or precludes re-treatment would appear to be a reasonable requirement of patients being treated with ustekinumab. It is noted too that this schedule of visits is less frequent than (or equally as frequent as) those for some other treatments for moderate to severe plaque psoriasis, e.g. phototherapy. These office visits would also permit an opportunity for the clinician to reinforce key safety considerations of which patients should remain mindful between visits.

Risk Assessment

Literature data indicates that inhibition of IL-12/IL-23 expression leads to an increased carcinogenic risk: systemic administration of IL-12 exhibits an anti-tumor effect in mice, inhibition of IL-12/IL-23 expression with a murine monoclonal antibody enhances tumor formation in mice challenged with squamous cell carcinoma cells and removal of the IL-12/IL-23 gene in knockout mice enhanced tumor formation in mice.

There is sufficient nonclinical data in the literature indicating an increased carcinogenic risk with inhibition of IL-12/IL-23 expression to justify inclusion in labeling of this animal data to inform prescribers about the potential carcinogenic risk from ustekinumab use. However, it is critically important that the applicant have a rigorous postmarketing program for assessing the risk of adverse events in patients, including adverse events reflective of immunosuppression, and, particular to the applicant's product, adverse events of malignancy. The risk assessment program should be comprehensive in scope and adequately designed to permit a determination of the risk of treatment with ustekinumab, e.g. serious adverse events, cardiovascular events, immunogenicity, etc. The applicant's proposed risk assessment program may not be adequate to accomplish these objectives.

A primary element of the applicant's risk assessment program is a multi-center, open registry of patients entitled the Psoriasis Longitudinal Assessment and Registry (PSOLAR). PSOLAR is a prospective, longitudinal, 8-year, observational study of long-term safety and clinical outcomes in patients at least 18 years of age with all forms of psoriasis, including plaque psoriasis and psoriatic arthritis, who are candidates for systemic therapy. The study is being conducted in both academic and community-based practices. The purpose of PSOLAR is to further evaluate the safety of a recombinant immunoglobulin G (IgG) biologic product, infliximab (Remicade, by the same sponsor, Centocor, Inc., and approved in August 24, 1998), in patients with chronic severe (extensive and/or disabling) plaque psoriasis and all overlapping forms of psoriasis, including plaque psoriasis and psoriatic arthritis, in patients who are candidates for systemic therapies; the applicant intends to extend the objective of PSOLAR to include evaluation of the safety of ustekinumab in patients with chronic severe psoriasis.

The protocol states that PSOLAR is designed to track serious adverse events, and targeted adverse events (such as malignancies, tuberculosis and other opportunistic infections, hypersensitivity-reactions, autoimmune disease, neurologic or demyelinating disease, congestive heart failure, hepatotoxicity, and hematologic events) in addition to disease activity, quality of life and specific health economic measures. The registry will enroll approximately 8,000 patients, to include at least 4000 infliximab-exposed patients, and a comparable number of patients who are prescribed other biologics or systemic therapies.

The primary objective of the registry is to evaluate the safety of infliximab in patients with chronic severe (extensive and/or disabling) plaque psoriasis and all overlapping forms of psoriasis, including plaque psoriasis and psoriatic arthritis, in patients who are candidates for systemic therapies. The secondary objectives of the registry are (1) to evaluate clinical outcomes, quality of life, and comorbidities for patients who may receive conventional systemic or biologic therapy for psoriasis, and (2) to assess the proportion of patients exposed to infliximab that meet labeling criteria relative to the number of patients exposed, based on data collected within the registry.

Per page 66 of the applicant's RMP, PSOLAR "is designed to specifically track AEs in approximately 8000 patients, of whom up to 4000 will be exposed to ustekinumab." Per page 188 of the sponsor's RMP and the www.clinicaltrials.gov listing for PSOLAR (<http://clinicaltrials.gov/ct2/show/NCT00508547?term=psolar&rank=1>. Accessed May 19, 2008), this registry is planned to include at least 4000 infliximab-exposed patients, and a comparable number of patients who are prescribed other biologics or systemic therapies.

Study Design: PSOLAR is proposed to be multicenter involving 500 sites in North America, Europe and Asia. This registry is a prospective, longitudinal, 8-year, observational study of long-term safety and clinical outcomes in patients receiving treatment for psoriasis. Treatment will be provided based on actual clinical practice or standard of care and there will be no restrictions on the use of concomitant medications. As noted under "6 Statistical Methods" of the PSOLAR registry protocol, data from the registry will be evaluated using longitudinal observational cohorts to assess safety, clinical outcomes, quality of life, comorbidities, pharmacoeconomics, and treatment regimens.

Data Collection: Patient demographics, medical history and baseline characteristics, medical history, past history of psoriasis treatments; history of concomitant medications, dose and frequency of infliximab or other systemic therapies, and clinical status will be collected at the time of enrollment, i.e., baseline and on a 6-monthly basis. The protocol states the reporting timeline for all adverse events including serious adverse events; adverse events of special interest which include malignancies; tuberculosis and opportunistic infections; hypersensitivity reactions; autoimmune disease; neurologic or demyelinating events; congestive heart failure; hepatotoxicity; and hematological events; and pregnancy will be within one week of observation or notification. With respect to deaths, the protocol states that all patient deaths must be reported to the sponsor or its

designee by the registry physician/site within 24 hours of observation or notification. Data will be obtained by direct contact with the patient, review of the medical records, contact with the patient's treating physician. The protocol states that the registry will be conducted in accordance with current ethical regulations and guidelines and informed consent will be obtained from all patients prior to data collection.

Duration of Observation: The protocol states that patient enrollment phase will last approximately 2 years; the planned observation period for each patient will be 8 years; and the registry will be conducted for a period of approximately 10 years.

Patient Follow-up and Retention: The protocol states that the patient participation in the registry will be encouraged but patients will have the right to voluntarily withdraw consent at any time.

Interim Analyses: The protocol states that interim analyses will be conducted annually and comprehensive annual report with registry accrual rates, number of adverse events, total person years of observation, psoriasis severity, dose and duration of therapy, as well as uptake of the infliximab and ustekinumab will be included. The protocol mentions the existence of a Registry Steering Committee.

Data Integrity: The protocol states that the sponsor or its designee will perform site visit during the course of the registry to monitor the progress of the registry; and maintain the overall quality and integrity of the data.

Risk Assessment Conclusion

Registries may be designed as complete (mandatory enrollment) or incomplete (voluntary enrollment). In general, incomplete registries such as PSOLAR may not represent the best research design to study long term and rare outcomes such as malignancies, and opportunistic infections due to limited absolute size, voluntary participation, and issues of loss-to- follow-up. As also acknowledged by the applicant "registries may not have the ability to evaluate rare events or identify lower relative risks." (Applicant's Briefing Document for Ustekinumab, May 13, 2008, p. 123).

The protocol for PSOLAR suggests that data will be compared with other conventional and biologic therapies.

In conclusion, PSOLAR may not be the best research design to study the long-term safety of ustekinumab. An alternative option could be a mandatory long-term registry where all individuals exposed to ustekinumab are included. Input from the Advisory Committee on the optimal approach would be useful.