DERMATOLOGIC AND OPHTHALMIC DRUGS
ADVISORY COMMITTEE MEETING
9 SEPTEMBER 2003

RAPTIVA™ (Efalizumab)

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The abbreviations used in this document are defined in Table 1 below.

Table 1

Abbreviations and Terms

Abbreviation	Definition
APC	Antigen-presenting cells
BLA	Biologics License Application
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
DLQI	Dermatology Life Quality Index
F	Female
FDA	Food and Drug Administration
FE	First Exposure (first 12 weeks of Raptiva treatment)
FT	First 12-week treatment period of controlled studies (2058, 2059, 2390, and 2600)
GI	Gastrointestinal
HLA-DR	Human leukocyte antigen-DR
HUVEC	Human vein endothelial cell
ICAM	Intercellular adhesion molecule
IL-2	Interleukin-2
ITT	Intent to treat
IV	Intravenous
LFA-1	Lymphocyte function–associated antigen-1
M	Male
MOA	Mechanism of action
NA	Not applicable
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NK	Natural killer
NMSC	Non-melanomatous skin cancer
NOS	Not otherwise specified
OLS	Overall Lesion Severity (now referred to as Physicians Global Assessment)

Table 1 (cont'd)

Abbreviations and Terms

Abbreviation	Definition
PASI	Psoriasis Area and Severity Index
PASI-50	50% improvement in PASI score relative to Day 0 of the first 12-week treatment period
PASI-75	$<$75% improvement in PASI score relative to Day 0 of the first 12-week treatment period
PGA of Change	Physician's Global Assessment of Change
PD	Pharmacodynamics
PK	Pharmacokinetics
PBMC	Peripheral blood mononuclear cell
PSA	Psoriasis Symptom Assessment
PTLD	Post-transplant lymphoproliferative disorder
qow	Every other week
SC	Subcutaneous
SD	Standard deviation
SEER	Surveillance, Epidemiology and End Results
SEM	Standard error of mean
SH	Saskatchewan Health
TCP	Thrombocytopenia
UHC	UnitedHealthcare
WBC	White blood cell

1. EXECUTIVE SUMMARY

Raptiva represents a novel approach to the treatment of moderate to severe psoriasis. It is a recombinant humanized monoclonal antibody that binds to lymphocyte cell surface marker CD11a, and it inhibits activation and trafficking of T-cells.

Raptiva has been extensively studied in 13 psoriasis clinical trials in which 2,762 subjects were treated with Raptiva. Four of the studies were placebo-controlled, randomized, Phase III trials. Subjects treated with Raptiva experienced rapid, clinically meaningful, and statistically significant benefits across every measured endpoint in all Phase II and III clinical studies. Subjects receiving Raptiva had fewer psoriatic skin lesions, less itching, and improved quality-of-life as well as sustained benefits while on therapy. Few subjects experienced serious adverse effects from Raptiva therapy; most adverse events were mild and transient. Below is a list of key conclusions drawn from the Raptiva clinical studies:

- Raptiva improves signs and symptoms of psoriasis:

  After 12 weeks of Raptiva treatment, 27% of subjects had PASI-75 improvement and 59% of subjects had PASI-50 improvement compared with placebo rates of 4% and 14%, respectively.

  All other secondary endpoints, including global psoriasis assessment (PGA), quality-of-life scale (DLQI), and itching scale, showed statistically and clinically significant benefit.

- Raptiva has an early onset of action, with reduction in PASI score demonstrated 4 weeks after the start of treatment.

- The beneficial effects of Raptiva are consistent across patient subgroups.

- The efficacy of Raptiva improves with continuous treatment past 12 weeks.

  After 24 weeks of Raptiva treatment, 44% of subjects had PASI-75 improvement and 66% of subjects had PASI-50 improvement.

- Raptiva is well tolerated, and its overall safety profile is favorable:

  The rate of serious adverse events was low (2% in the proposed to-be-marketed 1 mg/kg/wk dose group) and similar to the rate in placebo-treated subjects.

The most common adverse events were mild, self-limited, and associated with the first two doses. These events included headache, chills, nausea, fever, myalgia, and asthenia.

A small number of subjects (~1 in 500) had NCI Grade 3 or 4 thrombocytopenia that was reversible upon discontinuation of Raptiva. A causal relationship with Raptiva could not be ruled out.

There is no evidence to suggest that Raptiva affects the overall rate of malignancies and infections compared with placebo.

- Withdrawal of Raptiva results in a loss of benefit. In some subjects (~13%), rapid return of disease or a change in morphology was observed. Transition to other therapies after discontinuation largely reduces the occurrence of these adverse events.
- Raptiva maintains its favorable safety profile even with extended treatment.

1.1 PROPOSED INDICATION

Raptiva is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis.

1.2 EFFICACY

Primary support for the efficacy of Raptiva in moderate to severe plaque psoriasis is provided by the adequate and well-controlled Phase III study (2390) in subjects with moderate to severe plaque psoriasis. Supportive data come from the randomized, double-blind, placebo-controlled studies (2600, 2058, and 2059), which used the same basic eligibility criteria and design of the first 12-week treatment course as Study 2390.

Subjects participating in the Phase III, placebo-controlled studies all had a diagnosis of moderate to severe plaque psoriasis as defined by a score of at least 12 on the Psoriasis Area and Severity Index (PASI) and psoriatic involvement of at least 10% of body surface area (BSA). Subjects were required to be candidates for systemic psoriasis treatment or had to have received prior therapy with systemic treatments.

Raptiva treatment commenced with an initial dose of 0.7 mg/kg, followed by 11 weekly doses of 1.0 mg/kg. In Studies 2058 and 2059, subjects were also

randomized to receive 2.0 mg/kg Raptiva weekly during the first 12-week treatment period.

The primary efficacy endpoint was the proportion of subjects who achieved 75% or greater improvement from baseline in PASI (referred to as PASI-75) on Day 84. Secondary efficacy variables included the PASI-50, Physician's Global Assessments, a validated quality-of-life assessment—the Dermatology Life Quality Index (DLQI)—and other subject-reported assessments focusing on symptoms and itching.

In the pivotal study (2390), the PASI-75 and PASI-50 responses were statistically significantly higher for the Raptiva-treated group compared with the placebo-treated group ($p<0.001$; see Figure 1a). In all three supportive studies, the benefit of Raptiva treatment was consistent with that seen in Study 2390 and was statistically significant.

The efficacy of continuous treatment with 1.0 mg/kg/wk Raptiva beyond 12 weeks is demonstrated by data from the open-label extension study (2391), which allowed subjects who completed Study 2390 to continue Raptiva treatment for a further 12 weeks. The PASI-75 response rate increased from 27% at the end of 12 weeks of treatment to 44% at the end of 24 weeks of treatment ($p<0.001$; see Figure 1b). The percentage of subjects achieving a PASI-50 was also increased with a further 12 weeks of treatment.

Figure 1a

PASI Response at 12 Weeks of Treatment in Study 2390

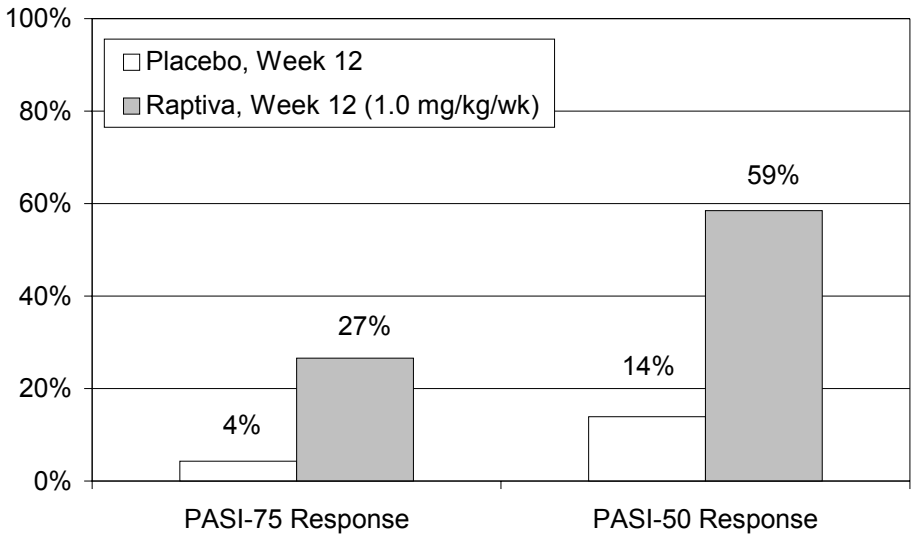
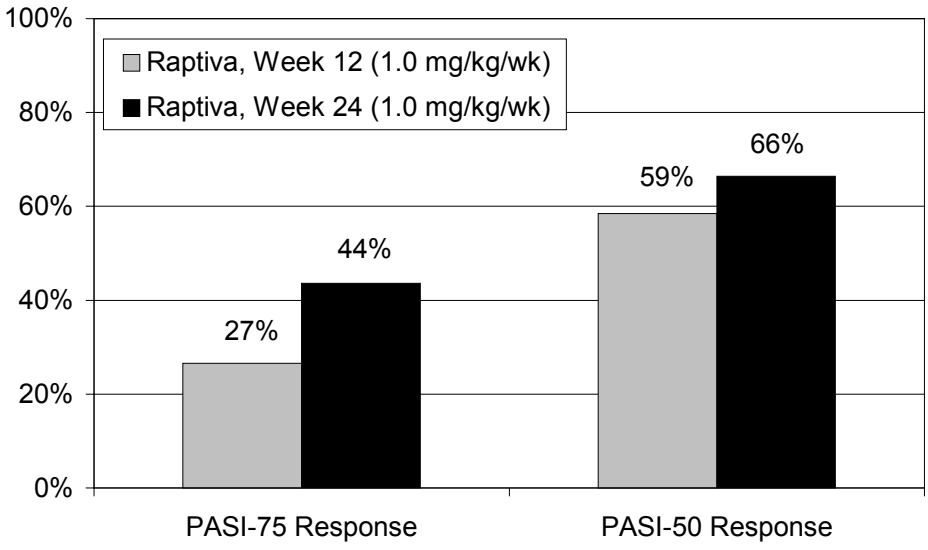


Figure 1b

PASI Response following 12 and 24 Weeks of Treatment
in Studies 2390 and 2391



The placebo rate for 24 weeks is not available because placebo-treated patients rolled over to Raptiva at 12 weeks.

The efficacy of Raptiva was consistent across patient subgroups. In particular, Raptiva appears to be equally effective in patients with moderate, severe, or very severe disease.

Raptiva has a rapid onset of action. In Study 2390, at Day 28 the mean PASI percent improvement from baseline was significantly greater ($p < 0.001$) in the Raptiva 1.0 mg/kg group compared with the placebo-treated group.

In addition, early response to treatment was observed in the quality-of-life measure, the DLQI: the mean improvement from baseline in DLQI was significantly greater ($p < 0.001$) by Day 28 (the first post-baseline assessment) in the Raptiva-treated group compared with the placebo-treated group. Further, for the Raptiva-treated subjects, the improvement at Day 28 had reached 70% of the total DLQI improvement achieved by Day 84, indicating a substantial early quality-of-life benefit.

1.3 SAFETY

Raptiva was studied in 2,762 subjects with psoriasis. Of these, 1,620 subjects were treated in the placebo-controlled, randomized Phase III trials.

During the first 12-week, placebo-controlled treatment period, the overall rate of adverse events was slightly higher for the Raptiva-treated groups compared with the placebo-treated group (73.6% in the placebo-treated group, 82.4% in the Raptiva 1.0 mg/kg/wk group, and 87.0% in the Raptiva 2.0 mg/kg/wk group). Headache, chills, fever, nausea, and myalgia were among the most frequently reported adverse events in the Raptiva-treated subjects. These events were part of “acute adverse reactions” that were predefined in the clinical program. The reactions were generally mild, self-limited, and short-lived and occurred most often with the initial two doses.

During the first 12-week, placebo-controlled treatment period, the overall rate of serious adverse events was low and similar between the placebo-treated group (1.7%) and the Raptiva 1.0 mg/kg/wk group (2.0%). Most types of serious adverse events were reported for a single subject, and no pattern of serious adverse events suggestive of toxicity was noted.

Overall rates of adverse events leading to discontinuation of treatment were low (2.5% for the 1.0 mg/kg/wk group compared with 2.0% for the placebo-treated group) over the first 12 weeks.

Malignancies were reported infrequently and occurred at comparable rates between the placebo-treated and Raptiva-treated groups. The overall incidence rate of malignancies per 100 subject-years was 1.62 in the placebo-treated group and 1.68 in the Raptiva-treated group.

The overall frequency of infections during the first 12 weeks was comparable between the placebo-treated group (26.3%) and the 1.0 mg/kg/wk Raptiva-treated group (28.9%). The rates of serious infections requiring hospitalization were low and relatively similar between the Raptiva- and placebo-treated groups (1.61 per 100 subject-years vs. 1.18 per 100 subject-years, respectively), and were consistent with the expected background rate based on external epidemiological data.

Clinical trials were designed such that Raptiva was discontinued without taper or transition to other therapies in the clinical program. In addition, use of other psoriasis medications was usually restricted even when subjects experienced return of psoriasis. Adverse events of psoriasis were experienced by 13.0% of the subjects during the 12-week period following discontinuation of Raptiva, most of which were mild to moderate in severity. Only 6 (0.5%) of 1,166 subjects who underwent Raptiva washout experienced a serious adverse event of psoriasis. In the subset of subjects who initiated psoriasis medications during treatment withdrawal, the rate of psoriasis adverse events was substantially lower.

Out of the 2,762 Raptiva-treated subjects in the clinical program, there were six reports of reversible NCI Grade 3 or 4 thrombocytopenia (TCP) that were consistent with a possible drug-induced effect. Four of the 6 subjects had received medications or had concurrent medical conditions that could have contributed or predisposed subjects to the onset of TCP. Although causality has not been established, these results suggest that reversible thrombocytopenia may occur infrequently (approximately 1 in 500 patients) in patients treated with Raptiva. However, the overall rate of TCP observed during Raptiva treatment appears less than that reported with other

treatments used in patients with moderate to severe psoriasis (e.g., NEORAL® [package insert]).

During the Raptiva program, there were no clinically significant differences in laboratory abnormalities observed between the Raptiva- and placebo-treated subjects. A total of 6.3% of the subjects developed anti-Raptiva antibodies, but almost all had extremely low titers. There were no clinically relevant safety or efficacy effects associated with the antibodies. Preliminary vaccination data suggest that secondary response to immunization may be reduced by Raptiva treatment. Studies are currently ongoing to evaluate immune responses during and following administration of weekly SC doses of Raptiva. The current recommendation is to hold Raptiva treatment for 4–8 weeks before an immunization.

Raptiva was well tolerated over the treatment periods beyond the initial 12 weeks. An examination of adverse events for subjects treated with Raptiva beyond the initial 12 weeks of treatment up to 1 year indicates no increase in the percentage of subjects reporting adverse events with longer Raptiva exposure and no change in the rate of serious adverse events.

1.4 CONCLUSIONS

Raptiva has been demonstrated to be safe and effective for the treatment of psoriasis. Raptiva has a rapid onset of action and is well tolerated over long durations of treatment. Extended therapy with Raptiva provides increased clinical efficacy with no increase in adverse events. Overall, there were few serious adverse events associated with Raptiva therapy, no evidence of organ toxicity, and no evidence of increased malignancies or infections.

Raptiva provides a significant new, safe, and efficacious alternative for patients with moderate to severe plaque psoriasis.

2. OVERVIEW

2.1 BACKGROUND

The clinical development of Raptiva was performed collaboratively by XOMA (Berkeley, CA) and Genentech, Inc. (South San Francisco, CA).

In December 2002, a Biologics License Application (BLA) was submitted. In May 2003, a Safety Update was provided to the Food and Drug Administration (FDA). Except where otherwise noted, the data in this briefing document are drawn from the BLA and the Safety Update.

2.2 PATHOPHYSIOLOGY OF PSORIASIS

Psoriasis is a T cell–mediated, inflammatory disease characterized by accumulation of activated T lymphocytes in the epidermis and dermis that stimulate hyperproliferation of keratinocytes to produce psoriatic lesions (see Figure 2) (Griffiths et al. 1995; Gottlieb 1998; Austin et al. 1999; Bos and De Rie 1999; Nickoloff 1999). The antigen that causes psoriasis is unknown, but the pathophysiology has been studied extensively, particularly with regard to T cells. In order to mediate the cellular changes in the dermis that lead to psoriasis, T lymphocytes first undergo three key interactions with other cell types.

Step 1: Antigen-presenting cells (APCs) must first be activated in the epidermis, where antigen is internalized, enzymatically processed, and presented on the APC surface. Activated APCs then travel to the regional lymph nodes, where they interact with naive T lymphocytes, resulting in T-lymphocyte activation.

Step 2: T-lymphocyte binding to venous endothelial cells occurs, followed by trafficking into dermal and epidermal tissue.

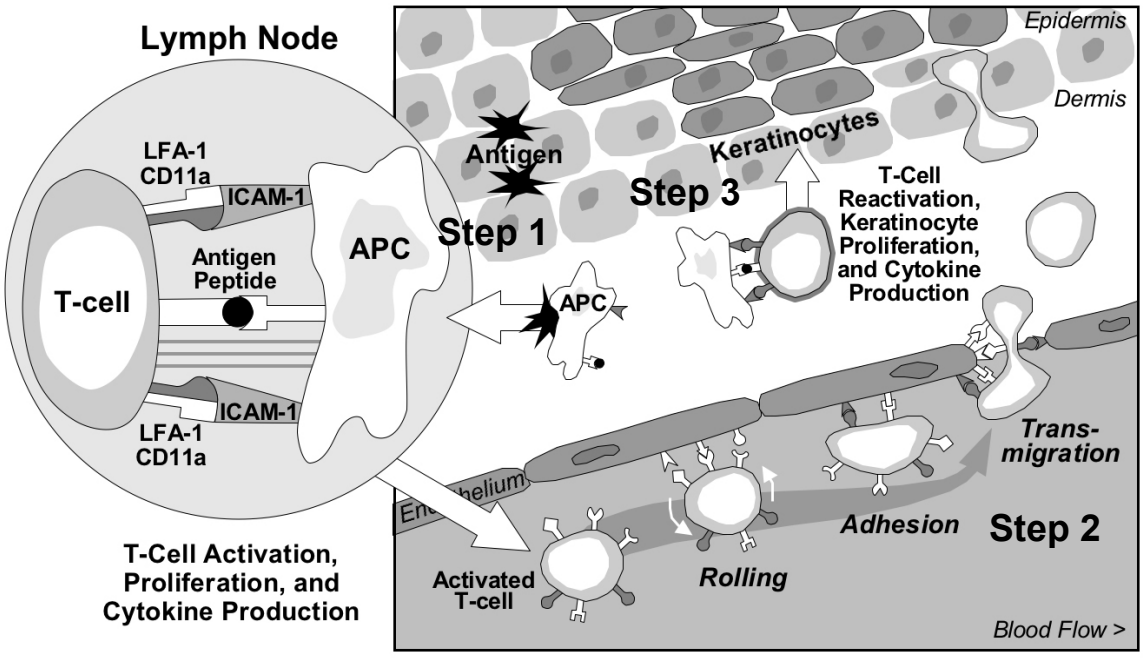
Step 3: T-lymphocyte reactivation by a second exposure to the specific antigen, which occurs in the dermis or epidermis. This leads to release of pro-inflammatory cytokines and other inflammatory mediators, which stimulate the increased keratinocyte proliferation.

Whereas Step 1 occurs only once, it is followed by proliferation of the activated T cells, providing an amplification of the process. Steps 2 and 3 occur in an iterative fashion, causing the persistence of the disease.

A large number of integrins and selectins on T lymphocytes contribute in their interaction with APCs or endothelial cells.

Figure 2

Psoriasis



Schematic based on Krueger JG. J Am Acad Dermatol 2002;46(1):1–23.

2.3 MECHANISM OF ACTION OF RAPTIVA

LFA-1 (lymphocyte function–associated antigen-1, a leukocyte cell surface protein) is an adhesion molecule whose expression is limited to leukocytes. LFA-1 is composed of two subunits: CD11a and CD18. Whereas CD18 is also part of other adhesion molecules, CD11a is unique to LFA-1. This restricted expression of CD11a limits the potential effects of Raptiva to cells that express LFA-1. Although LFA-1 is a key adhesion molecule, leukocytes express multiple other members of the integrin and selectin families.

Variation in distribution of these multiple adhesion molecules leads to variation in the relative functional importance of LFA-1. Binding of Raptiva to the CD11a subunit of LFA-1 inhibits LFA-1 function. Raptiva does not induce apoptosis or mediate cell killing. Effects of Raptiva on lymphocytes and other cell types are reversible.

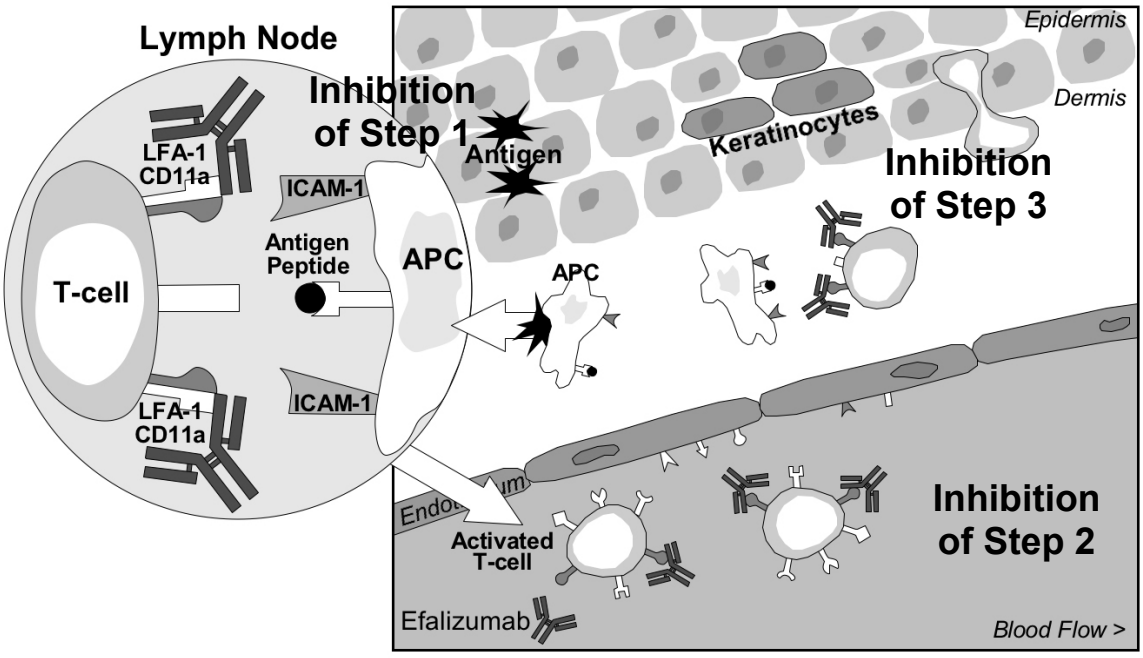
LFA-1 binds to members of the ICAM (intercelluar adhesion molecule) family. ICAM is expressed by APCs and is up-regulated on endothelial cells and keratinocytes in psoriasis plaques. Inhibition of LFA-1 function by Raptiva interferes in several key steps of psoriasis pathophysiology.

Raptiva inhibits adhesion of T lymphocytes to other cell types by inhibiting the binding of LFA-1 to ICAM-1 (see Figure 3). This mechanism of action (MOA) has a number of effects, depending on the cell type, including the following:

- Inhibition of T-lymphocyte activation (proliferation, cytokine release)
- Inhibition of T-lymphocyte trafficking and extravasation
- Inhibition of T-lymphocyte interactions with tissue-specific cells (keratinocytes)

Figure 3

Raptiva's Mechanism of Action



Treatment with Raptiva can potentially interfere at several critical points in the pathophysiology of psoriasis:

- Inhibition of initial activation of naive T cells in regional lymph nodes
- Inhibition of T-lymphocyte proliferation and interleukin-2 (IL-2) receptor expression
- Inhibition of T-lymphocyte trafficking to psoriatic lesions
- Inhibition of secondary T-lymphocyte activation in the dermis and epidermis
- Inhibition of T-lymphocyte interactions with keratinocytes
- Inhibition of T-lymphocyte release of cytokines that drive further inflammation within the psoriatic plaque

Projected actions of Raptiva were verified in skin biopsies from moderate to severe psoriasis subjects participating in the clinical trials. The number of infiltrating T cells in both the dermis and epidermis was decreased by Raptiva treatment. This was accompanied by decreased expression of inflammatory markers (decreased ICAM-1 and HLA-DR) and normalization of keratinocyte differentiation as reflected by keratin 16 expression. Epidermal and dermal thickness returned to the normal range. Raptiva treatment produced full morphological and immunohistochemical normalization of lesional psoriatic skin.

3. PHARMACOLOGY

3.1 CLINICAL PHARMACOLOGY OF RAPTIVA

3.1.1 Raptiva Pharmacodynamics

Binding of CD11a by Raptiva results in saturation of available CD11a binding sites on lymphocytes, down-modulation of cell surface CD11a expression on lymphocytes and elevation of peripheral blood lymphocytes. As documented in the Phase I dose-ranging studies, the extent and duration of these effects was dose-dependent.

At the proposed marketed dose of 1.0 mg/kg/wk SC, Raptiva produced maximal effects on pharmacodynamic markers, throughout the dosing interval i.e., reduced CD11a expression to ~15%–30% of baseline and saturated CD11a on T lymphocytes in the peripheral blood to $<5\%$ of baseline available binding sites. After cessation of treatment, CD11a expression returned to baseline as Raptiva was eliminated from the body. Similarly, Raptiva also affects other leukocyte populations, although the extent of maximal effect is different for the different subpopulations and less than that on T lymphocytes (see Table 2).

Table 2

Overall Maximal Effects for Down-Modulation of CD11a Expression and Saturation of Available CD11a Binding Sites on Leukocyte Subpopulations by Raptiva during Weekly Treatment in the Clinical Studies

Cell Type	CD11a Down-Modulation Measured by CD11a Expression (Percent Baseline) [a]	CD11a Saturation Measured by Available CD11a Binding Sites (Percent Baseline)
T lymphocyte ($CD3^+$)	15%–30%	$<5\%$
$CD4^+$ phenotype	10%–20%	$<5\%$
$CD8^+$ phenotype	20%–25%	$<5\%$
B lymphocytes	25%–50%	$<10\%$
NK cells	35%–50%	$<5\%$
Monocytes	60%–75%	$<10\%$
Neutrophils	45%–65%	$<10\%$

NK = natural killer.

[a] Ranges represent mean data from the last dosing interval in several multiple-dose studies.

Reduction in CD11a expression was rapid after intravenous (IV) and SC administration. The full effect on pharmacodynamic markers following SC administration was seen after 24–48 hours.

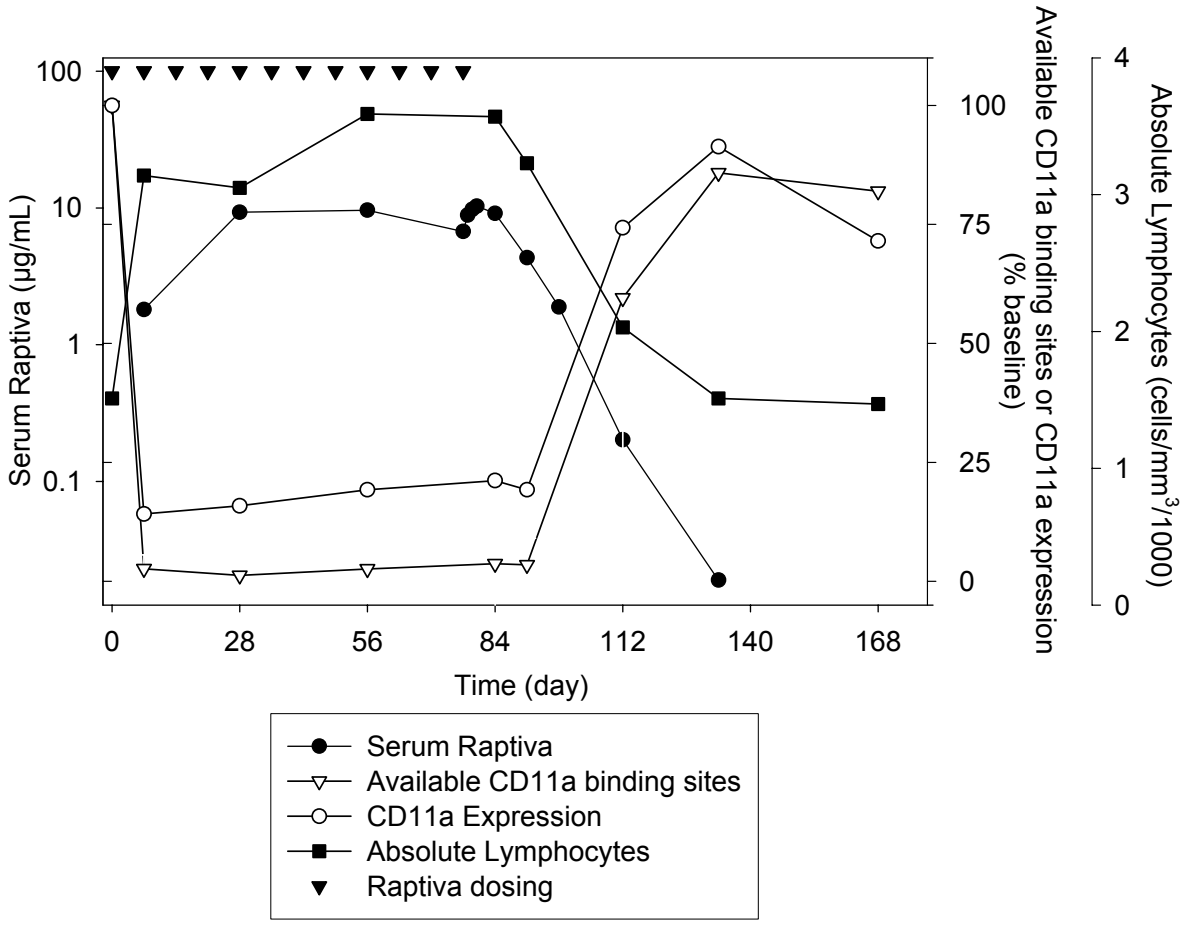
Multiple weekly IV doses of $\geq$0.3 mg/kg were required to maintain CD11a down-modulation between doses, whereas weekly IV doses of $\geq$0.6 mg/kg were required to maintain full CD11a saturation between weekly doses.

Multiple weekly SC doses of 1.0 mg/kg were required to maintain both CD11a down-modulation and saturation between doses. Limited data are available at SC doses of $<$1.0 mg/kg/wk.

Following the 12th and last dose of 1.0 mg/kg/wk SC, CD11a expression returned to baseline as Raptiva was cleared from circulation. Between 5 and 8 weeks following the last dose, mean CD11a expression was within 25% of baseline values (see Figure 4).

Figure 4

Mean Serum Raptiva Concentration (PK), CD11a Expression, and Available CD11a Binding Sites and Absolute Lymphocyte Counts (PD) following Administration of 1.0 mg/kg/wk Raptiva for 12 Weeks in Study 2142



PD = pharmacodynamics; PK = pharmacokinetics.

Increases in the absolute counts of circulating leukocytes were observed following administration of Raptiva. Absolute white blood cell (WBC) counts increased by 2.5–3.5 $\times 10^3$ cells/µL following 1.0 and 2.0 mg/kg/wk Raptiva to ~10 $\times 10^3$ cells/µL. The largest change occurred in the absolute count of circulating lymphocytes. T-lymphocyte and B-lymphocyte counts approximately doubled, whereas natural killer (NK) cell counts increased by ~50%. Increased counts were apparent within 24 hours of the first dose.

Leukocyte counts remained elevated with weekly dosing and returned to baseline after treatment cessation. The time course of the changes was closely related to the effects of Raptiva on CD11a expression and available CD11a binding sites. After administration of 1.0 mg/kg/wk for 12 weeks, lymphocyte levels returned to within 10% of baseline by 8 weeks following the last dose. Similar to the maximum effects on CD11a expression, maximum circulating leukocyte counts were comparable at doses of 1.0 and 2.0 mg/kg/wk.

3.1.2 Raptiva Pharmacokinetics

Raptiva showed dose-dependent nonlinear pharmacokinetics, which can be explained by its saturable specific binding to its cell surface receptor, CD11a.

Mean maximum concentration of drug was 12.4 and 30.9 μg/mL for the 1.0 and 2.0 mg/kg/wk doses, respectively; at steady state, peak concentrations were achieved by ~2 days after SC doses. The mean time from last dose to the time when Raptiva plasma concentrations fell below the limit of detection (0.019 μg/mL) was 25 and 44 days for the 1.0 and 2.0 mg/kg/wk doses, respectively.

With SC doses of 1.0 mg/kg/wk, relative bioavailability of Raptiva was ~50%.

Steady-state trough levels were achieved 4 weeks following administration of 1.0 mg/kg/wk and 8 weeks following administration of 2.0 mg/kg/wk, as assessed from Raptiva serum trough levels after weekly dosing.

In the Phase III Study 2390, mean $\pm$ standard deviation (SD) steady-state Raptiva trough levels at Day 84 were 11.1 ± 7.9 μg/mL ($n = 275$) following 12 weekly SC doses of Raptiva at 1.0 mg/kg. In subjects from this study, Raptiva reduced CD11a expression to 19% of baseline and saturated CD11a to $< 5\%$ of baseline available binding sites on T lymphocytes in the peripheral blood. Maximal effects observed in this study indicate that subjects achieved adequate exposure to Raptiva.

Consistent trough levels measured during five consecutive 12-week treatment periods in the 3-year extension study (2243) indicate that there was no unexpected accumulation during long-term treatment.

There was a 6.3% (67/1063 subjects) incidence of anti-Raptiva antibodies in subjects for whom serum samples were available during the follow-up period after elimination of Raptiva from serum. Anti-Raptiva antibody titers were low. There was an apparent decrease in efalizumab serum levels in subjects who had anti-Raptiva antibodies. Anti-Raptiva antibodies interfere with the efalizumab serum assay; therefore this decrease could be an artifact. Anti-Raptiva antibodies did not affect the pharmacodynamics since the peripheral blood lymphocytes stayed elevated and lymphocyte CD11a saturation was maintained. There was no impact on efficacy or safety (see Section 6.3).

Through population pharmacokinetic analyses, weight was found to be the most significant covariate affecting Raptiva SC clearance, confirming the validity of weight-based dosing. The population pharmacokinetic model indicated that the clearance of Raptiva was 24% lower at a dose level of 2.0 mg/kg/wk compared with 1.0 mg/kg/wk, consistent with dose-dependent nonlinear pharmacokinetics. The other pathophysiologic covariates of baseline PASI, baseline lymphocyte count, and age had only modest effects on clearance; sex and race had no effect on Raptiva clearance.

CD11a expression and saturation in peripheral blood are good biologic markers for adequate dosing based on three factors: 1) integration of CD11a expression in peripheral blood; 2) CD11a expression in skin (immunohistology); and 3) psoriasis disease assessment by PASI improvement. Mechanistically, the pharmacodynamic effect is related to maximal saturation of CD11a on peripheral blood T lymphocytes.

At Phase III doses (1.0 and 2.0 mg/kg/wk for 12 weeks SC), maximal effects were seen on these pharmacodynamic markers (i.e., CD11a was fully down-modulated and saturated).

No clinically meaningful relationship was found between steady-state Raptiva level (summarized by quartiles) and any measure of overall efficacy or safety events in the Phase III studies, which used doses of 1.0 and 2.0 mg/kg/wk.

3.1.3 Raptiva Immunology and Immunocompetence

T-lymphocyte proliferation was not impaired in vitro in the mixed lymphocyte reaction when using peripheral blood mononuclear cells (PBMCs) obtained from subjects receiving Raptiva treatment. The preparation of such PBMCs included washing procedures that removed Raptiva from T cells, suggesting that T lymphocytes rapidly regain their normal activation potential after drug removal or clearance.

A transient increase of CD69 expression (an early activation marker) on a small percentage of circulating T lymphocytes was observed after the first IV or SC dose of Raptiva and after subsequent IV doses when the previous dose was too low to maintain saturation of CD11a. No concomitant up-regulation of CD25 (a second early activation marker) or increases in cytokines typically produced by activated T lymphocytes were noted, suggesting that the $CD69^{+}$ T lymphocytes were not fully activated.

Adverse events (e.g., fever, chills, etc.) observed after the initial administration of Raptiva (first-dose effects) were accompanied by small transient increases in plasma levels of acute phase reactants such as IL-6, C-reactive protein, and fibrinogen. These changes were not associated with T-lymphocyte activation.

In a Phase I study (HU9602), subjects were vaccinated with bacteriophage ϕX174 1 day after receiving a single dose of Raptiva. The data from this study suggest that that secondary response to immunization may not be effective during Raptiva treatment, particularly at dose levels of >0.6 mg/kg IV (Gottlieb 1998).

Subjects did not experience a decrease or increase in preexisting serum concentrations of anti-cytomegalovirus or anti-tetanus toxoid antibodies after treatment. Secondary booster vaccinations in humans during Raptiva treatment are currently under investigation. The safety and efficacy of vaccines, specifically live or live-attenuated vaccines, administered to patients being treated with Raptiva have not been studied.

To study immune responses in greater detail, a Phase I, randomized, placebo-controlled, single-blind, parallel-group, single-center study (2244) is

in progress. Study 2244 is designed to evaluate immune responses during and following administration of 12 weekly SC doses of 1.0 mg/kg Raptiva in 60 adult subjects with moderate plaque psoriasis.

3.2 NONCLINICAL PHARMACOLOGY TOXICOLOGY DATA

Because of the species specificity of Raptiva in humans and chimpanzees and the limited availability of chimpanzees, a chimeric rat/mouse anti–mouse CD11a antibody (muM17), was developed and evaluated as a surrogate for Raptiva. Safety studies were performed with Raptiva in chimpanzees and with muM17, an anti–mouse CD11a antibody, in mice to provide a comprehensive safety evaluation.

The nonclinical pharmacology, pharmacokinetics, and toxicology of Raptiva are consistent with the binding of the antibody to its ligand, CD11a. All safety signals observed in the nonclinical safety evaluation of Raptiva or muM17 can be explained by the known immunomodulatory effects of these antibodies. These effects occurred at doses approximately equivalent to the clinical dose of 1.0 mg/kg/wk Raptiva.

Consistent with the pharmacologic activity of these antibodies, CD11a expression was greatly reduced on T cells in chimpanzees and mice treated with Raptiva and muM17, respectively. Similar effects have been seen in humans. The clinical relevance of the occasional overexpression of CD11a following clearance of Raptiva from the serum is unknown because no safety signals were observed in animals during this period of overexpression.

Both Raptiva and muM17 appear to alter the trafficking of lymphocytes such that there is a reduction in the cellularity of the lymph nodes, increased spleen weights (evaluable with muM17 in mice only), and increases in the circulating WBC count (noted with both Raptiva in chimpanzees and humans and with muM17 in mice). These changes do not appear to have any adverse toxicologic consequences.

In a developmental toxicity study conducted in mice using muM17, no evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed. No adverse effects on behavioral, reproductive, or growth parameters were

observed in offspring of female mice exposed to an anti-mouse CD11a antibody during gestation and lactation. At 11 weeks of age, the offspring had intact cell-mediated immunity and a reduction in the primary antibody response. At 25 weeks of age, the offspring had a normal primary antibody response.

In a fertility and general reproduction study with muM17, no adverse effects were noted on mating, fertility, or reproduction parameters in male and female mice.

A 6-month study was conducted in TSG-p53® wild-type mice, a strain shown to be susceptible to lymphoma development. Additionally, cyclosporine has been shown to produce lymphomas in this strain when mice were treated for a period of 6 months (Storer et al. 2001). The study was conducted to address the chronic safety of muM17 and to determine the potential for treatment-related effects on lymphoma development. Results of this study indicated that treatment of mice for 6 months with muM17 was well tolerated; there was no treatment-related increase in lymphomas whereas one lymphoma was observed in placebo-treated mice. Expected findings, including increased spleen weight and lymphoid organ changes, were consistent with trafficking/demargination changes related to the pharmacologic activity of the antibody. Additional long-term animal studies have not been conducted to evaluate the carcinogenic potential of Raptiva.

Raptiva was considered to be generally well tolerated in chimpanzees at doses of up to 40 mg/kg/wk IV for 6 months, providing an exposure ratio of 339-fold based on cumulative dose and 174-fold based on the cumulative area under the curve compared with a clinical dose of 1.0 mg/kg/wk for 12 weeks. The surrogate antibody, muM17, was also well tolerated in mice at doses up to 30 mg/kg/wk SC for 6 months, providing an exposure ratio of 10- to 25-fold based on plasma concentration compared with the clinical dose of Raptiva.

4. OVERVIEW OF CLINICAL TRIALS

Early evaluation of Raptiva was conducted in seven Phase I and II clinical studies. Data on the safety and efficacy of Raptiva were subsequently obtained from the pivotal study, 2390, which used the to-be-marketed product. This trial was conducted in adults (≥18 years old) with moderate to severe plaque psoriasis who were candidates for systemic therapy and who had a baseline PASI score of ≥12.0, with plaque psoriasis covering ≥10% of total BSA (Krueger et al. 2000). Extensive supportive data are provided in three additional Phase III placebo-controlled studies (2600, 2058, and 2059). Support for the long-term use of Raptiva is provided by the open-label study, 2391, which provides extended treatment for subjects treated in Study 2390, and also by Studies 2058 and 2059 and the ongoing open-label study, 2243. Support for retreatment and additional long-term continuous treatment data were obtained from Study 2062, which provided Raptiva treatment for subjects who had participated in earlier clinical trials.

There were five Phase I studies (HU9602, HUPS249, HUPSS254, HUPS256, and 2142) and one Phase II study (HUPS252) performed using Raptiva in the treatment of psoriasis. Two of the Phase I studies (HU9602 and HUPS249) and the Phase II study (HUPS252) used an IV formulation of Raptiva; the safety data for these three studies are not reviewed in this document except in the discussion of malignancy events. The safety data from three of the remaining four Phase I studies (HUPS254, HUPS256, and 2142), which used an SC formulation of Raptiva, are part of the pool of data from subjects in the first 12-week treatment period of the open-label and placebo-controlled studies. Table 3 summarizes the completed Phase I, II, and III psoriasis studies. Table 4 summarizes the ongoing studies.

Table 3

Clinical Development of Raptiva: Completed Psoriasis Studies

Type of Study	Study Number	Study Objectives	Study Design/ Type of Control	Route(s) of Administration	Number of Subjects [a]	Indication	Duration of Treatment
Phase I	HU9602	Safety, pharmacokinetics, and biologic activity	Open-label, single-dose	IV	31	Moderate to severe plaque psoriasis	Single dose
Phase I	HUPS249	Safety, pharmacokinetics, and biologic activity	Open-label, multiple-dose	IV	39	Moderate to severe plaque psoriasis	7 Weeks
Phase II	HUPS252	Safety and efficacy	Placebo-controlled, double-blind, randomized	IV	145	Moderate to severe plaque psoriasis	8 Weeks
Phase I	HUPS254	Safety and efficacy	Open-label, single- and multiple-dose	SC	57	Moderate to severe plaque psoriasis	Single dose and 8 weeks
Phase I	HUPS256	Safety, pharmacokinetics, and biologic activity	Open-label, randomized	SC and IV	77	Moderate to severe plaque psoriasis	12 Weeks
Phase III	2058	Efficacy, safety, and tolerability	Placebo-controlled, double-blind, randomized	SC	498	Moderate to severe plaque psoriasis	12–24 Weeks
Phase III	2059	Efficacy, safety, and tolerability	Placebo-controlled, double-blind, randomized	SC	597	Moderate to severe plaque psoriasis	12–24 Weeks
Phase III	2062	Safety and tolerability of retreatment	Open-label	SC	536	Moderate to severe plaque psoriasis	12 Weeks

[a] Includes all study participants treated with Raptiva or placebo. Some subjects participated in more than one study.
[b] An additional subject was randomized, but not treated.

Table 3 (cont'd)

Clinical Development of Raptiva: Completed Psoriasis Studies

Type of Study	Study Number	Study Objectives	Study Design/ Type of Control	Route(s) of Administration	Number of Subjects [a]	Indication	Duration of Treatment
Phase I	2142	Pharmacokinetics, pharmacodynamics, safety, and tolerability of Genentech Raptiva	Open-label	SC	70	Moderate to severe plaque psoriasis	12 Weeks
Phase III	2390	Efficacy, safety, and tolerability of 1.0 mg/kg	Placebo-controlled, double-blind, randomized	SC	555 [b]	Moderate to severe plaque psoriasis	12 Weeks
Phase III	2391	Safety of 1.0 mg/kg/wk in subjects who were previously treated with Raptiva or placebo in Study 2390	Open-label (extension of Study 2390)	SC	516	Moderate to severe plaque psoriasis	24 Weeks
Phase III	2600	Efficacy, safety, and tolerability of 1.0 mg/kg	Placebo-controlled, double-blind, randomized	SC	685 [b]	Moderate to severe plaque psoriasis	12 Weeks

[a] Includes all study participants treated with Raptiva or placebo. Some subjects participated in more than one study.

[b] An additional subject was randomized, but not treated.

Table 4

Clinical Development of Raptiva: Ongoing Psoriasis Studies

Type of Study	Study Number	Study Objectives	Study Design/ Type of Control	Route(s) of Administration	Number of Subjects [a]	Indication	Duration of Treatment
Phase III	2243	Safety, tolerability, and efficacy of prolonged maintenance treatment	Open-label, randomized	SC	339	Moderate to severe plaque psoriasis	12–132 Weeks
Phase I	2244	Immune response after 12 weekly doses of 1.0 mg/kg Raptiva	Placebo-controlled, single-blind, randomized	SC	60	Moderate psoriasis	12 Weeks
Phase III	2601	Safety of 1.0 mg/kg/wk in subjects who were previously treated with Raptiva or placebo in Study 2600	Open-label (extension of Study 2600)	SC	653	Moderate to severe plaque psoriasis	48 Weeks
Phase IIIb	HUPS300	Transition from SC Raptiva therapy to approved systemic and/or phototherapy for psoriasis	Open-label	SC	~120	Moderate to severe plaque psoriasis	12 Weeks

[a] Includes all study participants treated with Raptiva or placebo. Some subjects participated in more than one study.

5. CLINICAL EFFICACY

5.1 OVERVIEW OF STUDY 2390

5.1.1 Study 2390

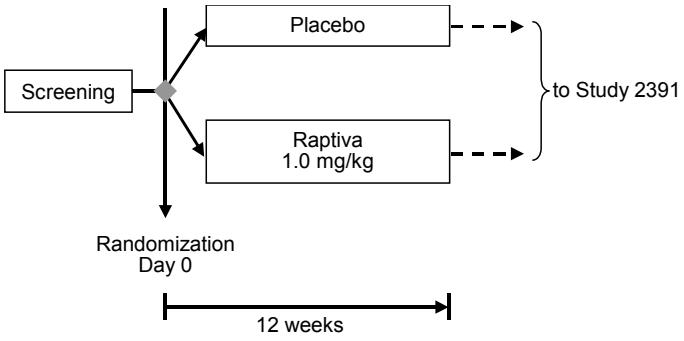
Study 2390 was a Phase III, randomized, double-blind, parallel-group, placebo-controlled, multicenter trial designed to evaluate the efficacy and safety of Raptiva (as the to-be-marketed product) in subjects with moderate to severe plaque psoriasis who were candidates for systemic therapy.

a. Study Design and Treatment

Following a 2- to 4-week screening period, eligible subjects were randomized in a 2:1 ratio to receive SC treatment with either 1.0 mg/kg/wk Raptiva or placebo equivalent for 12 weeks (see Figure 5). (During the first 12 weeks of treatment, subjects received an initial dose of 0.7 mg/kg followed by 11 weekly SC doses of 1.0 mg/kg.) Subjects were to return 1 week after the last SC treatment for Day 84 assessments. Randomization was stratified within study center using the Day 0 PASI score (≤ 16.0, ≥ 16.1) and prior treatment for psoriasis (naive to systemic treatment vs. prior systemic treatment).

Figure 5

Study 2390



The only concomitant psoriasis treatments allowed during the study were emollients, tar or salicylic acid preparations for scalp psoriasis, and low-potency (Grade VI or VII) topical corticosteroids if needed for lesions on the face, hands, feet, axillae, or groin. Oral antihistamines were allowed if

needed for pruritus. Thus, the results are representative of Raptiva monotherapy.

b. Study Population

Adults with plaque psoriasis covering ≥10% of total BSA and a PASI score of ≥12.0 who were either candidates for systemic psoriasis therapy or had a history of receiving systemic therapy were randomized into the study. A total of 556 subjects were enrolled at 29 sites in the United States and Canada.

c. Efficacy Outcome Measures

The primary efficacy endpoint was the proportion of subjects with a ≥75% improvement in PASI relative to baseline (PASI-75) at the end of 12 weeks of treatment referred to as PASI responders. PASI is a physician-performed assessment of both the extent of psoriasis on the four body areas (head, trunk, upper limbs, and lower limbs) and the degree of plaque erythema, scaling, and thickness (Fredriksson et al. 1983). The PASI score accounts for both the extent of BSA affected by the erythema, scaling, and thickness and the severity of the erythema, scaling, and thickness. The possible scores range from 0 (no disease) to 72 (maximal disease) (see Appendix B).

Observations on the PASI were corroborated by two Physician's Global Assessment scales:

- A static Physicians Global Assessment (PGA) reflecting the appearance of the subject on the day of observation, with rankings ranging from very severe to clear (see Appendix C)

  During the clinical studies this assessment was known as Overall Lesion Severity (OLS) scale. The principal secondary endpoint was the proportion of subjects rated as minimal or clear at the end of 12 weeks of treatment on this scale.

- A dynamic Physician's Global Assessment (PGA) of Change, ranging from worse to cleared (see Appendix D)

  This scale reflects a global assessment of the degree of improvement from baseline. Photographs obtained at baseline, clinic notes, and other materials were used by the investigator as desired in making this assessment. The endpoint was the proportion of subjects rated as excellent or cleared at the end of 12 weeks of treatment.

Other secondary endpoints were mean improvement in the thickness component of the PASI score, mean improvement in the percentage of BSA affected by psoriasis, proportion of subjects with $\geq$50% improvement in PASI score relative to baseline after 12 weeks of treatment (PASI-50), and mean percent PASI improvement over time. The following patient-reported scales were used: the Itching Scale, Dermatology Life Quality Index (DLQI), and frequency and severity subscales of the Psoriasis Symptom Assessment (PSA). Developed for the Raptiva trials, the PSA rates frequency and severity for eight symptoms of psoriasis and is similar to the Skindex (Chren et al. 1996). All subject-reported outcomes were assessed as change from baseline after 12 weeks of treatment.

d. Demographic and Baseline Characteristics

Demographic and baseline characteristics for all randomized subjects are summarized in Table 5. Overall, the two treatment groups were comparable with regard to demographic and baseline characteristics, with no statistically significant differences noted.

Table 5

Demographic and Baseline Characteristics
of Randomized Subjects in Study 2390

Characteristic	Placebo (n = 187)	Raptiva (n = 369)	All Subjects (n = 556)
Sex, n			
Male	132 (70.6%)	251 (68.0%)	383 (68.9%)
Female	55 (29.4%)	118 (32.0%)	173 (31.1%)
Race/ethnicity, n			
White	167 (89.3%)	331 (89.7%)	498 (89.6%)
Hispanic	7 (3.7%)	17 (4.6%)	24 (4.3%)
Other [a]	13 (7.0%)	21 (5.7%)	34 (6.1%)
Age group (yr), n			
18–40	68 (36.4%)	140 (37.9%)	208 (37.4%)
41–64	106 (56.7%)	206 (55.8%)	312 (56.1%)
≥65	13 (7.0%)	23 (6.2%)	36 (6.5%)
Age (yr)			
Mean (SD)	44.9 (11.8)	45.3 (12.8)	45.2 (12.5)
Range	20–75	18–75	18–75
Weight (kg)			
Mean (SD)	94.3 (18.8)	93.5 (20.6)	93.8 (20.0)
Range	50–143	45–160	45–160
Height (cm) [b]			
Mean (SD)	172.9 (10.1)	172.7 (10.4)	172.7 (10.3)
Range	147–196	123–198	123–198
BMI (kg/m^2) [b]			
Mean (SD)	31.54 (5.70)	31.43 (6.78)	31.47 (6.43)
Range	20.9–48.4	19.0–56.4	19.0–56.4
Tobacco use, n			
Never	61 (32.6%)	117 (31.7%)	178 (32.0%)
Previous	60 (32.1%)	113 (30.6%)	173 (31.1%)
Current	66 (35.3%)	139 (37.7%)	205 (36.9%)

BMI = body mass index.

[a] The "Other" group included individuals who described their race/ethnicity as Asian or Pacific Islander, Black, American Indian or Alaskan Native, or Other.

[b] Data were available for 551 subjects: 185 in the placebo-treated group and 366 in the Raptiva-treated group.

The two treatment groups were comparable at baseline with regard to the state of their psoriasis, with no statistically significant differences noted (see Table 6).

Table 6

Baseline Psoriasis Characteristics of Treated Subjects in Study 2390

Characteristic	Placebo (n = 187)	Raptiva (n = 369)	All Subjects (n = 556)
Duration of psoriasis (yr)	n = 187	n = 364	n = 551
Mean (SD)	19.3 (11.1)	19.3 (11.9)	19.3 (11.7)
Range	1–53	1–62	1–62
Prior systemic therapy, n			
Yes	139 (74.3%)	283 (76.7%)	422 (75.9%)
No	48 (25.7%)	86 (23.3%)	134 (24.1%)
PASI category, n			
≤ 16.0	83 (44.4%)	155 (42.0%)	238 (42.8%)
16.1–30.0	88 (47.1%)	181 (49.1%)	269 (48.4%)
> 30.0	16 (8.6%)	33 (8.9%)	49 (8.8%)
PASI score			
Mean (SD)	19.36 (7.41)	19.41 (7.52)	19.40 (7.47)
Range	11.4–50.3	10.1–58.7	10.1–58.7
PASI thickness component			
Mean (SD)	6.18 (2.33)	6.19 (2.43)	6.19 (2.40)
Range	2.8–14.5	2.4–18.8	2.4–18.8
PGA, n			
Minimal	1 (0.5%)	1 (0.3%)	2 (0.4%)
Mild	12 (6.4%)	23 (6.2%)	35 (6.3%)
Moderate	96 (51.3%)	206 (55.8%)	302 (54.3%)
Severe	69 (36.9%)	121 (32.8%)	190 (34.2%)
Very severe	9 (4.8%)	18 (4.9%)	27 (4.9%)
DLQI	n = 183	n = 363	n = 546
Mean (SD)	11.80 (6.87)	11.97 (6.42)	11.91 (6.57)
Range	0.0–30.0	0.0–30.0	0.0–30.0
Itching Scale	n = 187	n = 368	n = 555
Mean (SD)	6.2 (2.5)	6.4 (2.5)	6.4 (2.5)
Range	0–10	0–10	0–10
PSA frequency	n = 185	n = 361	n = 546
Mean (SD)	14.12 (5.27)	14.34 (5.30)	14.27 (5.29)
Range	2.0–24.0	2.0–24.0	2.0–24.0
PSA severity	n = 185	n = 362	n = 547
Mean (SD)	14.97 (5.43)	14.83 (5.65)	14.88 (5.57)
Range	2.0–24.0	0.0–24.0	0.0–24.0
Percent BSA of psoriasis			
Mean (SD)	27.33 (16.22)	28.29 (17.04)	27.97 (16.76)
Range	10.0–90.0	10.0–95.0	10.0–95.0

e. Subject Disposition

A total of 556 subjects were enrolled and randomized into the study: 187 subjects in the placebo-treated group and 369 subjects in the 1.0 mg/kg/wk Raptiva-treated group.

A total of 36 subjects (6.5%) discontinued treatment (see Table 7).

Table 7

Subject Disposition and Reasons for Discontinuation of Treatment in Study 2390

Subject Status	Placebo (n = 187)	Raptiva (n = 369)	All Subjects (n = 556)
Completed treatment	175 (93.6%)	345 (93.5%)	520 (93.5%)
Discontinued treatment	12 (6.4%)	24 (6.5%)	36 (6.5%)
Reason for discontinuation			
Subject's decision	3 (1.6%)	7 (1.9%)	10 (1.8%)
Adverse event	2 (1.1%)	7 (1.9%)	9 (1.6%)
Lost to follow-up	5 (2.7%)	4 (1.1%)	9 (1.6%)
Use of excluded medication	0	5 (1.4%)	5 (0.9%)
Investigator's decision	2 (1.1%)	1 (0.3%)	3 (0.5%)

The primary reason cited for discontinuation was subject's decision, followed by adverse events. The proportion of subjects who chose to discontinue was similar in the placebo-treated and Raptiva-treated groups.

f. Efficacy Results

PASI-75. The proportion of PASI-75 responders was statistically significantly greater in the Raptiva-treated group than in the placebo-treated group ($p < 0.001$; see Table 8). A 22.3% treatment effect (i.e., the difference in the proportion of responders between the Raptiva-treated group and the placebo-treated group) was observed, with a 95% confidence interval (CI) of 15.8%–29.5%.

Table 8

PASI-75 Response to Treatment at 12 Weeks for Randomized Subjects in Study 2390

PASI Response	Placebo (n = 187)	Raptiva (n = 369)
PASI-75	8 (4.3%)	98 (26.6%)
Fisher's exact p-value Raptiva vs. placebo	—	< 0.001
Treatment effect	22.3%	
95% CI for treatment effect	15.8%, 29.5%	

Note: Subjects whose Day 84 (Week 12) PASI score was missing were considered PASI-75 non-responders.

A more detailed examination of the distribution of percent improvement in PASI achieved at Day 84 demonstrates a general shift toward improvement in the Raptiva-treated group compared with a minimal change in the placebo-treated group. There was a greater proportion of subjects who experienced a PASI worsening at Day 84 compared with baseline (i.e., < 0% improvement from baseline) in the placebo-treated group (21.4%) than in the Raptiva-treated group (6.5%) (see Table 9).

Table 9

PASI Response at 12 Weeks as Percent Improvement from Baseline in Study 2390

	Percent Improvement from Baseline	Placebo (n = 187)	Raptiva (n = 369)
Improvement	≥ 90%	1 (0.5%)	19 (5.1%)
	≥ 75% to < 90%	7 (3.7%)	79 (21.4%)
	≥ 50% to < 75%	18 (9.6%)	118 (32.0%)
	≥ 25% to < 50%	39 (20.9%)	59 (16.0%)
	≥ 0% to < 25%	70 (37.4%)	48 (13.0%)
Worsening	≥ –25% to < 0%	32 (17.1%)	15 (4.1%)
	≥ –50% to < –25%	5 (2.7%)	6 (1.6%)
	< –50%	3 (1.6%)	3 (0.8%)
	Missing [a]	12 (6.4%)	22 (6.0%)

[a] Subjects with missing Day 84 (Week 12) PASI scores were classified as non-responders.

The majority of subjects receiving Raptiva (58.5%) experienced ≥ 50% improvement from baseline in PASI score compared with 13.9% of subjects receiving placebo.

Improvement occurred in each of the three key morphologic characteristics of psoriasis lesions (thickness, erythema, and scaling) as measured by improvement in the corresponding components of the PASI score. The mean improvement in the PASI thickness component at Day 84 relative to Day 0 was statistically significantly greater for subjects in the Raptiva-treated group compared with subjects in the placebo-treated group ($p < 0.001$). The mean improvement (decrease) from baseline for the Raptiva-treated group was at least three times that observed for the placebo-treated group. Although they were not formal endpoints of the study, the mean percent improvement in erythema and scaling corresponded closely to the mean percent improvement in thickness.

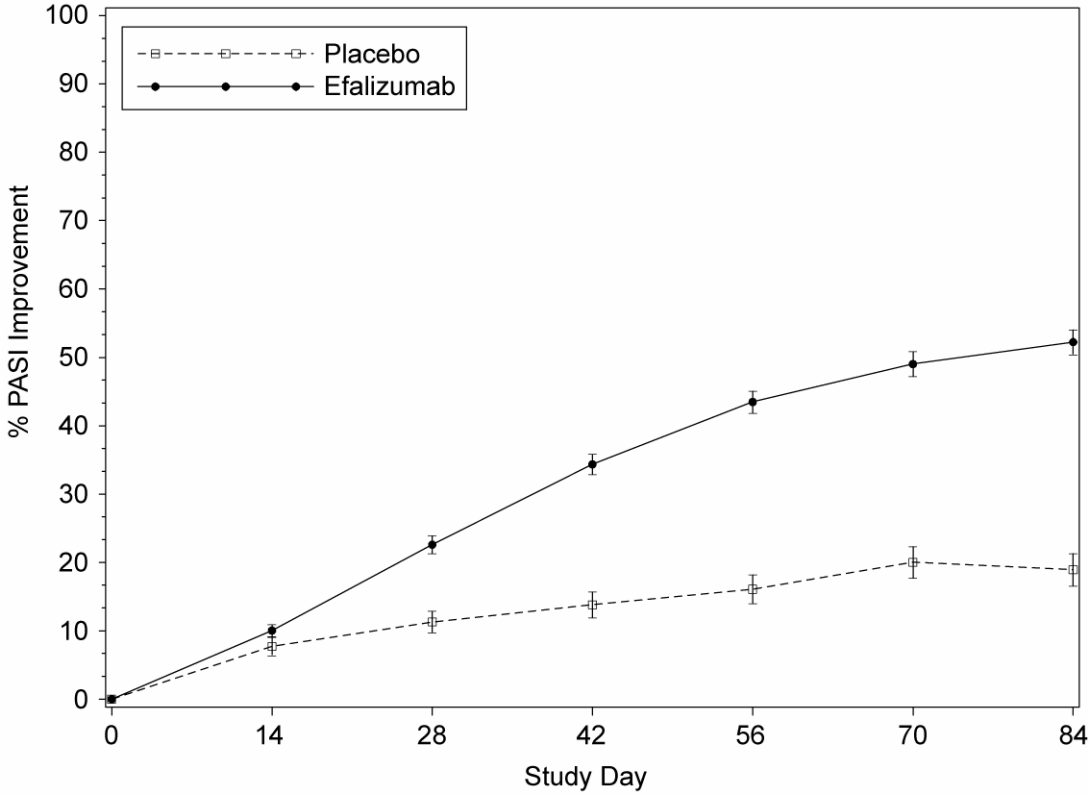
In addition, mean psoriatic BSA declined from 28% to 17% in subjects receiving Raptiva compared with a decline from 27% to 25% in those

receiving placebo ($p < 0.001$). Thus, Raptiva improves all of the cardinal features of psoriasis that contribute to the overall PASI score.

Subjects in the Raptiva-treated group showed a significant mean percent improvement in PASI score versus the placebo-treated group as early as 28 days following initial treatment ($p < 0.001$). The mean percent improvement in PASI score is presented over time for each treatment group in Figure 6.

Figure 6

Mean ± SEM Percent Improvement in PASI Score over Time in Study 2390



SEM = standard error of mean.

PGA. The proportion of subjects with a PGA rating of minimal or clear in the Raptiva-treated group (95 of the 369 subjects; 25.7%) was statistically significantly higher than that in the placebo-treated group (6 of the 187 subjects; 3.2%) ($p < 0.001$; see Table 10).

Table 10

PGA Response at 12 Weeks for Subjects in Study 2390

PGA Response	Placebo (n = 187)	Raptiva (n = 369)
Minimal or clear	6 (3.2%)	95 (25.7%)
Mild to very severe [a]	181 (96.8%)	274 (74.3%)
Fisher's exact p-value Raptiva vs. placebo	—	< 0.001

[a] Included subjects who were classified as mild, moderate, severe, and very severe and those whose Day 84 (Week 12) PGA rating was missing.

DLQI. A comparison of improvement from baseline in the DLQI overall scores at Day 84 for the Raptiva-treated group with the placebo-treated group was performed using the Wilcoxon rank-sum test. A decrease in DLQI overall scores represents improvement in dermatologic-related functionality and subject well-being. The improvement in mean DLQI overall scores was statistically significant in favor of the Raptiva-treated group compared with the placebo-treated group ($p < 0.001$; see Table 11). The improvement in the DLQI overall scores for the Raptiva-treated group was at least three times that observed for the placebo-treated group.

Table 11

Improvement from Baseline in Overall DLQI Score at Week 12 in Study 2390

DLQI	Placebo (n = 187)	Raptiva (n = 369)
Day 0		
n	183	363
Mean (SD)	11.8 (6.9)	12.0 (6.4)
Median	11.0	11.0
Range	0 to 30	0 to 30
Day 84 (Week 12) [a]		
n	187	368
Mean (SD)	10.2 (7.1)	6.4 (6.7)
Median	9.0	4.0
Range	0 to 30	0 to 30
Improvement from baseline [b]		
n	183	363
Mean (SD)	1.6 (5.7)	5.6 (6.6)
Median	1.0	5.0
Range	–13 to 25	–22 to 25
Wilcoxon rank-sum test p-value Raptiva vs. placebo	—	< 0.001

[a] The last observation carried forward was used to impute missing Day 84 (Week 12) DLQI values.

[b] Improvement was reflected by a decrease in overall DLQI score.

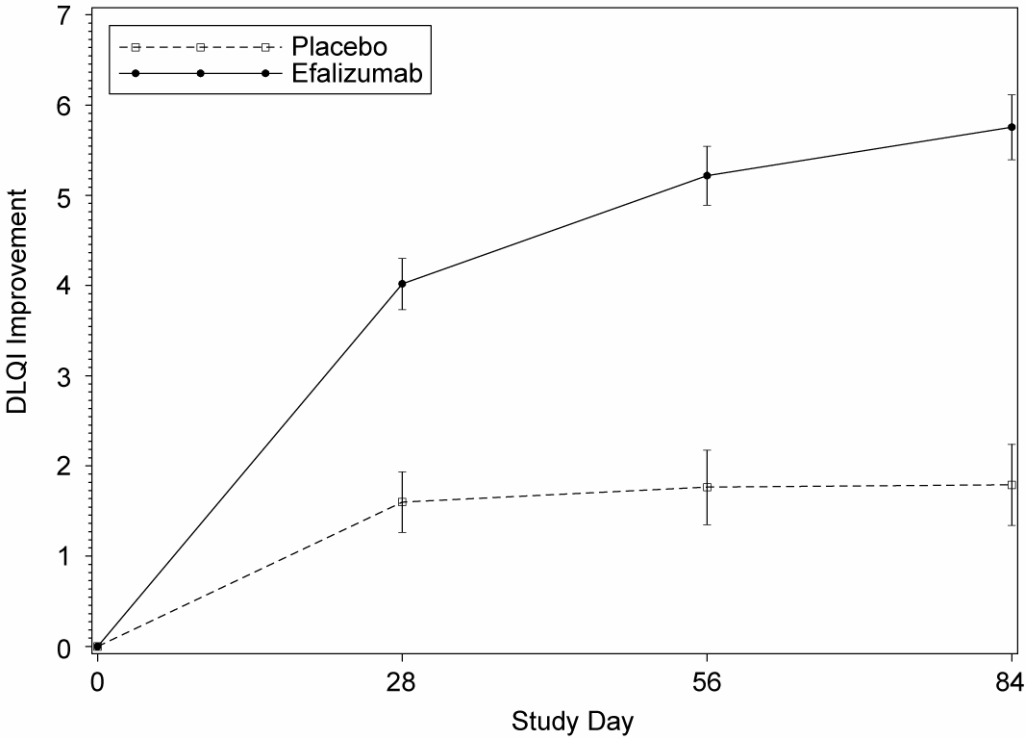
There was a consistent trend toward a treatment effect across all DLQI subscales (symptoms and feelings, daily activities, leisure, work and school, personal relationships, treatment).

Subjects in the Raptiva-treated group showed a clear improvement in DLQI scores versus the placebo-treated group at the first post-baseline assessment 28 days following initial treatment ($p < 0.001$; see Figure 7). In addition, for the Raptiva-treated subjects, the mean improvement in DLQI scores at Day 28 was 70% of the mean improvement at Day 84, indicating an early quality-of-life benefit.

Comparison of the pattern of improvement over time in DLQI in Figure 7 versus that for PASI in Figure 6 suggests that subjects perceive a quality-of-life benefit earlier than the physical improvement assessed by the physician through the PASI.

Figure 7

Mean ± SEM Improvement in DLQI over Time in Study 2390



SEM = standard error of mean.

Itching Scale. The mean improvement in the Itching Scale at Day 84 relative to Day 0 was statistically significant in favor of the Raptiva-treated group relative to the placebo-treated group ($p < 0.001$; see Table 12).

Table 12

Mean (SD) Improvement from Baseline in the Itching Scale at Week 12 in Study 2390

Change in Itching Score	Placebo (n = 187)	Raptiva (n = 369)
Day 0	6.2 (2.5)	6.4 (2.5)
Day 84 (Week 12) [a]	5.6 (2.7)	3.6 (2.9)
Improvement [b]	0.7 (2.8)	2.8 (3.3)
Two-sample t-test p-value Raptiva vs. placebo	—	< 0.001

[a] The last observation carried forward was used to impute missing Day 84 (Week 12) Itching Scale values.

[b] Improvement was reflected by a decrease in the score on the 10-point Itching Scale.

As observed for the PASI and DLQI, subjects in the Raptiva-treated group showed a clear improvement in mean Itching Scale scores versus the placebo-treated group at the first post-baseline assessment 28 days following initial treatment ($p < 0.001$).

PSA. A comparison of improvement from baseline in the frequency and severity of the psoriasis-specific symptom scores at Day 84 for the Raptiva-treated group versus the placebo-treated group was performed using the Wilcoxon rank-sum test. A decrease in PSA score represents improvement. Comparisons of the improvement from baseline in the Raptiva-treated group versus the placebo-treated group were statistically significant for both frequency of symptoms ($p < 0.001$) and severity of symptoms ($p < 0.001$), implying an improvement in psoriasis-specific symptoms for the Raptiva-treated group relative to placebo. The mean improvements in symptom frequency and severity in the Raptiva-treated group were more than two times those observed in the placebo-treated group.

Subjects in the Raptiva-treated group showed a clear improvement in both mean PSA frequency and mean PSA severity scores versus the placebo-treated group at the first post-baseline assessment 28 days following initial treatment ($p < 0.001$).

5.2 SUPPORTIVE STUDIES PROVIDING ADDITIONAL EFFICACY DATA

5.2.1 Study 2600

a. Study Design and Treatment

Study 2600 was a Phase III, randomized, double-blind, parallel-group, placebo-controlled, multicenter study designed to evaluate the safety of Raptiva (as the to-be-marketed product) administered at weekly SC doses of 1.0 mg/kg in subjects with moderate to severe plaque psoriasis who were candidates for systemic therapy. Subjects were required to have a psoriatic BSA of $\geq$10% and PASI $\geq$12.0 to be eligible for study enrollment.

Following a screening period, eligible subjects were randomized in a 2:1 ratio to receive SC treatment with 0.7 mg/kg for 1 week followed by 11 weeks of either 1.0 mg/kg/wk Raptiva or placebo equivalent. Subjects were to return 1 week after the last SC treatment for Day 84 assessments.

A total of 686 subjects were randomized in an approximate 2:1 ratio to receive either 12 weeks of 1.0 mg/kg/wk SC Raptiva or placebo equivalent at 58 sites in the United States and Canada. Of these subjects, 236 subjects were in the placebo-treated group and 450 subjects were in the Raptiva-treated group.

b. Efficacy Results

Efficacy endpoints were considered of secondary importance in this safety study. Efficacy was assessed by determining the proportion of subjects achieving PASI-75, PASI-50, and PGA ratings of clear or minimal (see Table 13). The treatment effect for the PASI-75 endpoint (i.e., the difference in the proportion of PASI-75 responders between the two groups) was 20.6%, with a 95% CI of 15.3%–26.6%.

Table 13

Efficacy Results at 12 Weeks for Randomized Subjects in Study 2600

Response	Placebo (n = 236)	Raptiva 1.0 mg/kg/wk (n = 450)	p-value [a] Raptiva 1.0 mg/kg/wk vs. Placebo
PASI-75	7 (3.0%)	106 (23.6%)	< 0.001
PASI-50	33 (14.0%)	234 (52.0%)	< 0.001
PGA clear or minimal	10 (4.2%)	91 (20.3%)	< 0.001

[a] Statistical comparisons were made between placebo-treated subjects and all Raptiva-treated subjects using Fisher's exact test.

Raptiva treatment also resulted in a statistically significant improvement in subject-reported symptoms of psoriasis as measured by the PSA. The mean improvements in symptom frequency and severity in the Raptiva-treated group were at least three times those observed in the placebo-treated group ($p < 0.001$ for separate comparisons of PSA frequency, PSA severity, and both itching components of the PSA).

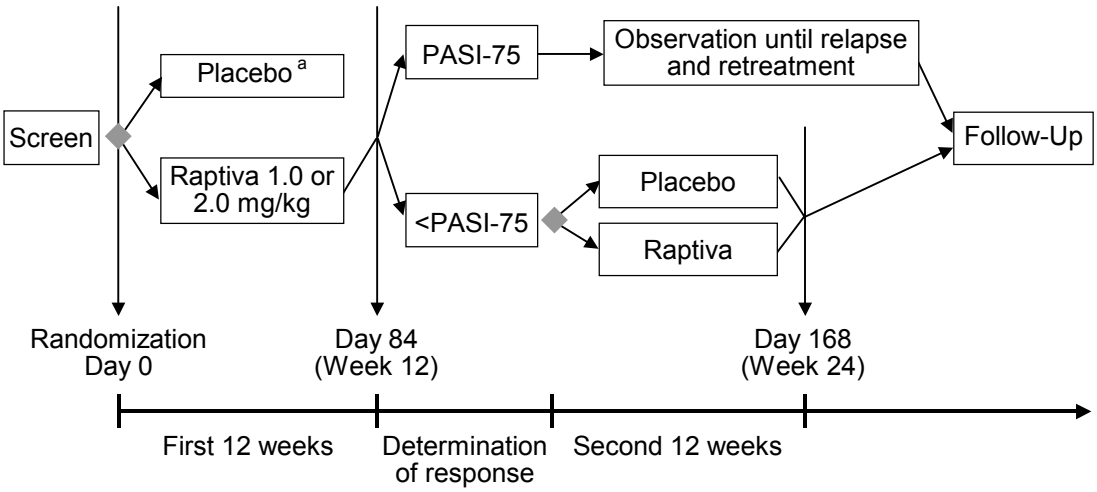
5.2.2 Study 2058

a. Study Design and Treatment

The first 12 weeks of Study 2058 were almost identical in design to the first 12 weeks of Study 2390. The study consisted of first treatment, observation, retreatment, and extended treatment periods, as well as a follow-up period (see Figure 8). The study was performed with a version of the product that will not be marketed.

Figure 8

Study 2058



◆=Randomization

[a] Placebo-treated subjects received a subsequent 12 weeks of treatment with Raptiva.

During the first 12 weeks of treatment, subjects received a conditioning dose of 0.7 mg/kg followed by 11 weekly SC doses of 1.0 mg/kg (low-dose) Raptiva (n=162), 2.0 mg/kg (high-dose) Raptiva (n=166), or placebo equivalent to low-dose or high-dose Raptiva (n=170 combined).

b. Efficacy Results for the First 12 Weeks of Treatment

The primary efficacy endpoint was the proportion of subjects with a PASI-75 response at the end of the first 12 weeks of treatment. The principal secondary endpoint was the proportion of subjects with a PGA rating of minimal or clear at the end of 12 weeks of treatment. Other secondary efficacy endpoints were percentage of subjects with a PGA of Change of cleared or excellent, time to relapse after the Day 84 visit for the FT period for subjects who achieved PASI-75 at the Day 84 visit, mean improvement in the thickness component of the PASI, mean improvement in the Itching Scale, and mean improvement in the BSA affected by psoriasis.

At Day 84, statistically significantly more subjects in the 1.0 mg/kg/wk group (38.9%) and the 2.0 mg/kg/wk group (26.5%) exhibited a PASI-75 response compared with the placebo-treated group (2.4%; $p<0.001$). The proportion of

subjects with a PGA rating of minimal or clear in the 1.0 mg/kg/wk group (32.1%) and the 2.0 mg/kg/wk group (22.3%) was statistically significantly higher than that in the placebo-treated group (2.9%; $p < 0.001$). Similar statistically significant differences in favor of each Raptiva-treated group over placebo ($p \leq 0.001$) were observed for all secondary efficacy endpoints tested. For subjects with a PASI-75 response, the median time to relapse (loss of $\geq 50\%$ of the improvement in the PASI score achieved between Day 0 and Day 84) was 67 days after the last Raptiva dose.

Results for treatment periods beyond the initial 12 weeks of treatment are presented in Section 5.4.

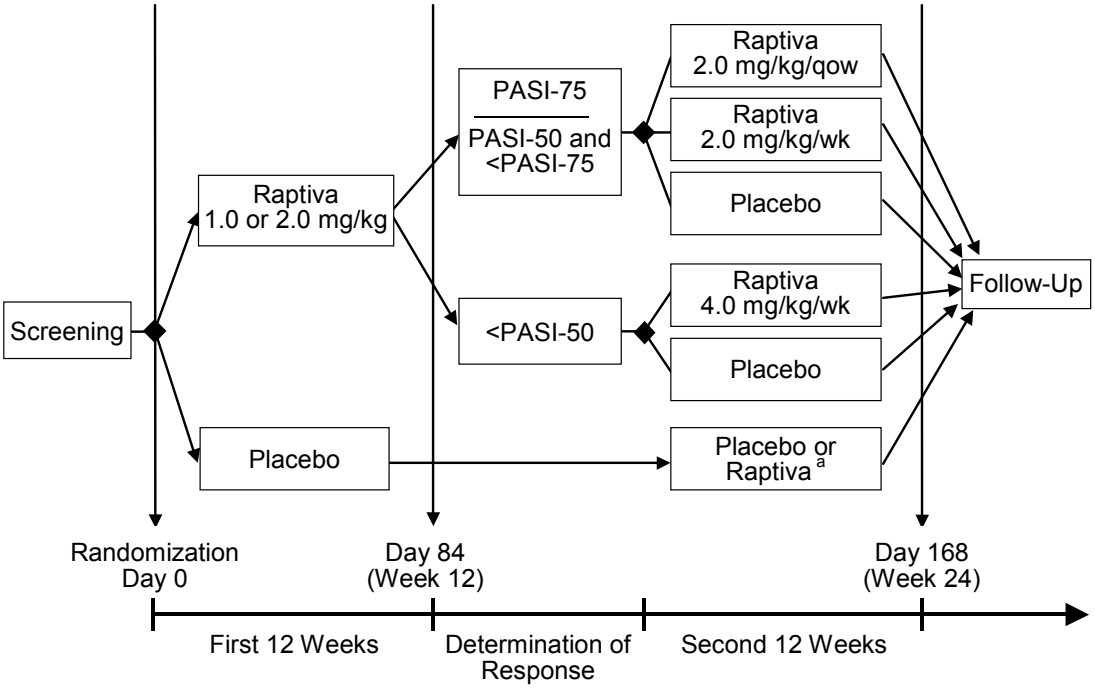
5.2.3 Study 2059

a. Study Design and Treatment

The first 12 weeks of Study 2059 were also almost identical in design to the first 12 weeks of Study 2390. Following a screening period, eligible subjects were randomized in a 2:1 ratio to a conditioning dose of 0.7 mg/kg followed by 11 weekly SC doses of 1.0 mg/kg Raptiva ($n = 232$), 2.0 mg/kg Raptiva ($n = 243$), or to placebo ($n = 122$). The study consisted of first treatment (12 weeks) and extended treatment (12 weeks) periods, as well as a follow-up period (see Figure 9). The study was performed primarily with a version of the product that will not be marketed.

Figure 9

Study 2059



◆=Randomization

[a] Placebo-treated subjects with <PASI-75 response received a subsequent 12 weeks of treatment with Raptiva.

b. Efficacy Results for the First 12 Weeks of Treatment

The primary efficacy endpoint was the proportion of subjects with a PASI-75 response at the end of 12 weeks of treatment. The principal secondary endpoint was the proportion of subjects with a PGA rating of minimal or clear at the end of 12 weeks of treatment. Other secondary efficacy endpoints were percentage of subjects with a PGA of Change of cleared or excellent, mean improvement in the thickness component of the PASI, mean improvement in the Itching Scale, and mean improvement in the BSA affected by psoriasis.

At Day 84, statistically significantly more subjects in the 1.0 mg/kg/wk group (22.4%) and the 2.0 mg/kg/wk group (28.4%) had a PASI-75 response compared with the placebo-treated group (4.9%; $p < 0.001$). The proportion of subjects with a PGA rating of minimal or clear in the 1.0 mg/kg/wk group (19.4%) and the 2.0 mg/kg/wk group (22.6%) was statistically significantly

higher than that in the placebo-treated group (3.3%; $p < 0.001$). Similar statistically significant differences in favor of each Raptiva-treated group over placebo ($p < 0.001$) were observed for all secondary efficacy endpoints.

Results for treatment periods beyond the initial 12 weeks of treatment are presented in Section 5.4.

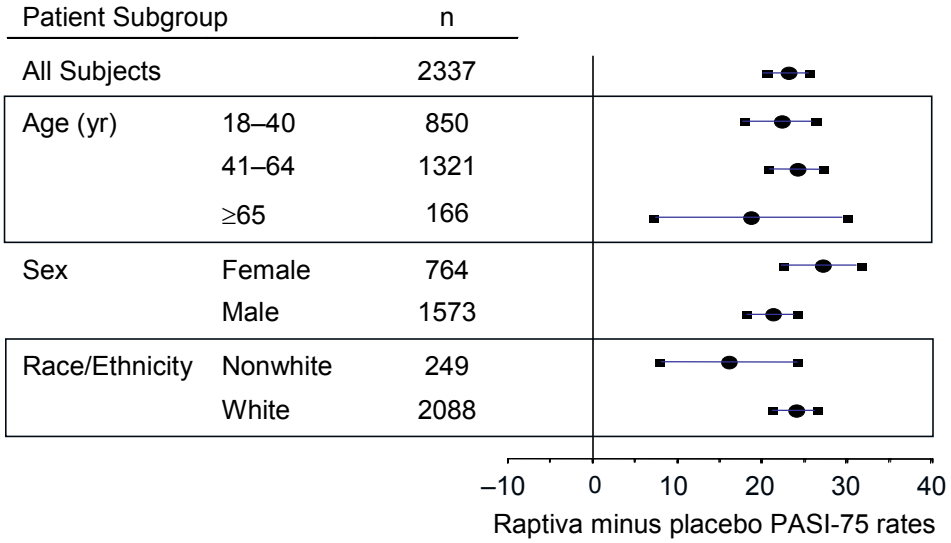
5.3 COMPARISON OF RESULTS IN SUBPOPULATIONS

The difference between the Raptiva and placebo PASI rates at Day 84 was summarized by subpopulations using pooled data from the first 12 weeks of treatment in the four placebo-controlled, Phase III trials (2058, 2059, 2390, and 2600).

Treatment effect for subgroups defined using demographic factors of age, sex, and race is displayed in Figure 10. As an example of what is plotted in the figure, the pooled placebo PASI-75 rate was 4% and the pooled Raptiva rate was 27%. The difference, 23%, is plotted as the circle in the top row. The 95% confidence interval in this case is approximately 20%–26%, which is plotted as the squares in the first row. Across the subgroups, the estimated treatment effect is similar, and the 95% confidence intervals are all to the right of the vertical line at zero, demonstrating the efficacy of Raptiva in each subgroup.

Figure 10

Raptiva Minus Placebo PASI-75 Rates at Day 84 by Demographic Subgroups (95% CI)

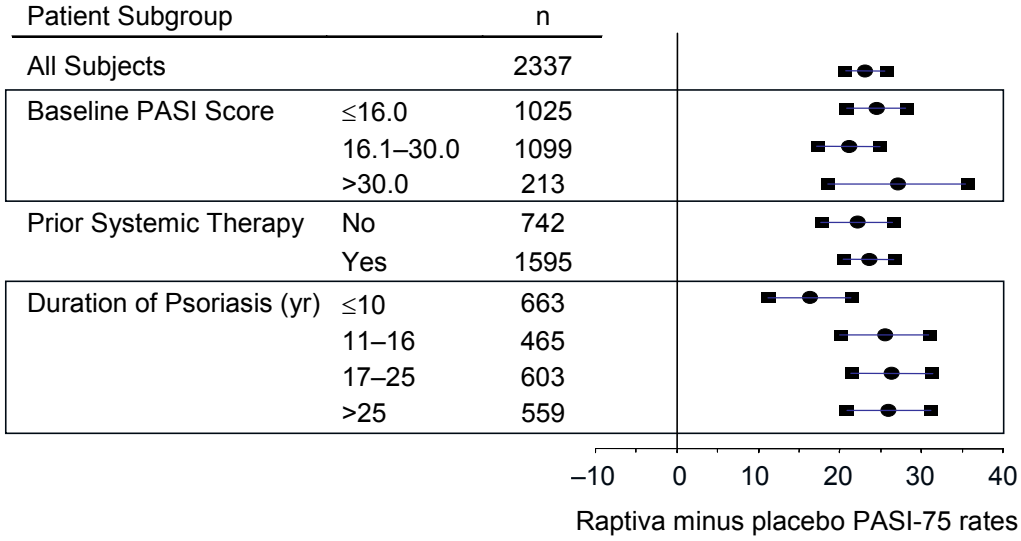


For each subgroup, the solid circle is plotted at the difference between the Raptiva and placebo PASI-75 rates, and the squares span the 95% confidence interval.

Treatment effect for subgroups defined using disease-related factors of baseline PASI, history of systemic therapy, and duration of disease is displayed in Figure 11. Again, estimated treatment effect is similar across each of the subgroups, and the 95% confidence intervals are all to the right of zero, demonstrating the efficacy of Raptiva in each subgroup. Importantly, Raptiva is equally effective in patients with moderate, severe, and very severe disease.

Figure 11

Raptiva Minus Placebo PASI-75 Rates at Day 84 by Disease-Related Subgroups (95% CI)



For each subgroup, the solid circle is plotted at the difference between the Raptiva and placebo PASI-75 rates, and the squares span the 95% confidence interval.

In addition, the difference between the Raptiva and placebo PASI-75 response rate was also consistent across patient subgroups based on season of treatment, subject weight, and subject body mass index.

5.4 TREATMENT BEYOND 12 WEEKS

a. Extended Treatment: Weeks 12–24

Study 2391. The efficacy of continuous treatment with 1.0 mg/kg/wk Raptiva beyond 12 weeks is demonstrated by combined data from Study 2390 and an uncontrolled, open-label study, 2391, which allowed subjects who completed the Phase III, randomized, placebo-controlled Study 2390 to continue Raptiva treatment beyond the initial 12 weeks (see Table 14). Efficacy was examined in an intent-to-treat (ITT) analysis of the cohort of subjects randomized to Raptiva in Study 2390. The PASI-75 response rate at the end of this second 12 weeks of treatment reached 44% from 27% at the end of the first 12 weeks of treatment in Study 2390.

Table 14

PASI-75 and PASI-50 Responses after 24 Weeks of Continuous Treatment for Subjects: Study 2391

PASI Response [a]	Group 2390-A (n = 369) [b]
PASI-75	161 (43.6%)
95% CI of response rate	38.5%, 49.0%
PASI-50	245 (66.4%)
95% CI of response rate	61.3%, 71.2%

[a] Subject who discontinued early from Study 2390 or 2391 were classified as non-responders.

[b] This group consisted of subjects who were randomized to receive Raptiva in Study 2390.

Studies 2058 and 2059. In Studies 2058 and 2059, many subjects who had received Raptiva for the first 12-week treatment period entered the Extended Treatment period and received a second course of 12 weekly SC doses of Raptiva or placebo (see Figures 8 and 9). The results from this second 12 weeks of treatment in Studies 2058 and 2059 were consistent with those seen in the data from Study 2391. In both studies, continued treatment with Raptiva was demonstrated to be superior to discontinuation.

b. Treatment beyond 24 Weeks

Long-term response to treatment with Raptiva is being evaluated in the ongoing, open-label study, 2243. Subjects were treated with 2.0 mg/kg/wk Raptiva for the first 12 weeks. The design of this study stipulated that only subjects achieving a PASI-50 response or a PGA rating of mild or better were allowed to continue treatment beyond the initial 12 weeks of treatment. Dosing in these subjects is decreased to 1.0 mg/kg/wk at the beginning of the subsequent Maintenance Treatment period; if a subject experiences relapse, the Raptiva dose is escalated to 2.0 mg/kg/wk for the remaining treatment period. Of the 339 subjects who started the study, 289 achieved a level of response that allowed them to receive continuous treatment past 12 weeks.

Response rates for cohorts of subjects entering sequential 12-week treatment courses are presented in Table 15.

Table 15

Treatment beyond 24 Weeks, Overview of Efficacy by PASI Response in Study 2243: PASI Response from Baseline during First and Extended Treatment (>12 Weeks) with Raptiva

Study	Week 12	Week 24	Week 36	Week 48
2243				
n [a]	339	289	269	243
PASI-75	140 (41.3%)	149 (51.6%)	159 (59.1%)	152 (62.6%)
ITT analysis of PASI response data [b]				
n	339	339	339	339
PASI-75	140 (41.3%)	149 (44.0%)	158 (46.6%)	152 (44.8%)

ITT = intent to treat.

[a] The population comprises all enrolled subjects for the first 12 weeks. After 12 weeks, the population includes only original enrollees who achieved PASI-50 or PGA ratings of mild, minimal, or clear at Week 12. Population changes between Week 24 and subsequent 12-week segments are due to subject discontinuations.

[b] This ITT analysis assumes that all subjects who discontinued from the study would remain <PASI-75 for each subsequent 12-week treatment period.

In assessing the long-term results presented in Table 15, it is recognized that all subjects with continuous dosing beyond 12 weeks did so as subsets of the original psoriatic population at baseline. In Study 2243, only subjects who achieved a PASI-50 response or a PGA rating of mild or better at the end of first 12-week treatment period were provided an opportunity for further continuous dosing to Week 48. In addition to the response rates by 12-week treatment segment presented in Table 15, a conservative ITT analysis was performed by assuming that all subjects who did not continue beyond the 12-week treatment period and all post–first treatment dropouts remained <PASI-75. The Week 24 to Week 48 response rates by this conservative method were higher than the Week 12 value of 41.3% (ranging from 44.0% to 46.6%).

c. Retreatment during Active Relapse

In Study 2058, subjects who achieved a PASI-75 response at the end of the initial 12-week treatment period then entered an untreated observation period. These subjects were followed until they experienced a protocol-defined relapse of disease, defined as a loss of ≥50% of the Week 12 improvement in

PASI score. The median time to relapse was 67 days from the last Raptiva dose.

At the time of relapse, subjects were randomized to double-blind placebo or Raptiva during a 12-week retreatment period. At the end of the retreatment period, 30.9% of Raptiva-treated subjects re-achieved a PASI-75 versus none of the placebo-treated subjects ($p < 0.001$), demonstrating the efficacy of Raptiva in the treatment of patients with active relapse of their disease.

Because all the subjects given Raptiva retreatment had been PASI-75 responders to the first 12 weeks of treatment with Raptiva, the re-treatment PASI-75 rate of 30.9% suggests a possible attenuation of the original response. However, the psoriatic state of subjects at the beginning of retreatment was very different from that of subjects at the beginning the first treatment period.

Subjects beginning retreatment were in active relapse, in contrast to the stability of subjects beginning first treatment after observation during screening. The worsening PASI scores of patients entering retreatment did not stabilize, on average, until after 14 days of retreatment, with improvements seen subsequently. After first treatment in subjects with stable disease, PASI scores improved, on average, after the first 14 days of treatment (see Figure 6).

This suggests that an intervening recurrence of disease did not appreciably attenuate the subsequent response to treatment, but that retreatment during a phase of rapid worsening is expected to require additional time to demonstrate a stable efficacy response of the magnitude observed after first treatment.

Further support that the efficacy of Raptiva on retreatment is similar to that of first treatment is provided by data from Study 2062, as described in the next section.

d. Other Retreatment Experience

In Study 2062, subjects who had participated in prior studies of Raptiva were allowed to receive retreatment with Raptiva. Prior exposure to Raptiva

ranged from a single IV dose to 12 weeks of SC Raptiva. Entry into the Study 2062 was not restricted based on PASI or percent BSA of psoriasis at baseline.

In the 364 subjects retreated with Raptiva in Study 2062, 25.3% achieved a PASI-75 response and 56.9% achieved a PASI-50 response, indicating that response to retreatment is similar to response to initial Raptiva treatment, as seen in the Phase III placebo-controlled studies.

A further analysis of Study 2062 data was performed in order to mimic the analysis of the Study 2058 retreatment period, but remove the effect of relapse on the results. For this analysis, subjects who met the following two criteria were selected:

- Subjects were PASI-75 responders to Raptiva treatment for 12 weeks in their previous study
- Subjects were enrolled in Study 2062 with >67 days between their first dose of Raptiva in Study 2062 and their last dose in the previous study. The cutoff of 67 days was chosen because this was the median time to relapse prior to the retreatment period in Study 2058

PASI-75 and PASI-50 responses were then determined at the end of Study 2062 relative to the PASI baseline of the first 12-week treatment period in the previous study.

There were 86 subjects who met the two criteria above. The PASI-75 rate was 61.6%, and the PASI-50 rate was 84.9%. These rates are substantially larger than those observed in the retreatment period of Study 2058 and demonstrate the maintenance of efficacy of Raptiva upon retreatment.

5.5 CLINICAL EFFICACY CONCLUSIONS

During the first 12 weeks of treatment, statistically significant results favoring Raptiva over placebo were achieved for the primary efficacy endpoint and all secondary endpoints ($p<0.001$ for each comparison). Significant improvement was also seen in all physician-assessed (PGA of Change, PASI thickness, and psoriatic BSA) and patient-reported (DLQI, Itching Scale, PSA frequency and severity) outcome measures.

Improvement in PASI was rapid. Significant improvement in PASI was noted in Raptiva-treated subjects compared with placebo-treated subjects 4 weeks after initiation of treatment in Study 2390 ($p < 0.001$). In addition, subjects in the Raptiva-treated group showed a clear improvement in mean DLQI scores, mean Itching Scale scores, mean PSA frequency, and mean PSA severity scores compared with the placebo-treated group at the first post-baseline assessment 4 weeks following initial treatment ($p < 0.001$).

Efficacy was consistent across subgroups. Similar efficacy was seen in subject groups defined by age, sex, body habitus, history of systemic therapy, duration of disease, season, region, and baseline PASI score.

Continued treatment with Raptiva maintained the improvements achieved during the initial 12 weeks of Raptiva treatment and was associated with further improvement as indicated by a PASI-75 response rate of approximately 44% after 24 weeks of continued treatment in Study 2390 and its extension, Study 2391.

6. CLINICAL SAFETY

6.1 OVERVIEW

A total of 2,762 subjects have been treated with Raptiva in the psoriasis clinical program. Of these, 1,620 subjects received Raptiva during the 12-week, placebo-controlled portion of the four Phase III studies (2390, 2600, 2058, and 2059). The nearly identical entry criteria and design of the first 12-week, placebo-controlled period support an analysis of the pooled data from the first 12 weeks of these studies. Comparisons between placebo and Raptiva patients are based primarily on this 12-week period.

Long-term safety is supported by data from 1,115 subjects who received more than 12 weeks of Raptiva treatment. Two hundred and twenty-eight of these subjects received weekly injections for 1 year.

The adverse events that occurred at low frequency are examined using data combined from all of the subcutaneous Raptiva studies. Incidence rates for these events are presented by subject-years of observation. In the current safety database, there are 186 subject-years of observation for subjects who received placebo and 1,791 subject-years of observation for subjects who received Raptiva. Because these observation periods were not concurrent and the average observation time per subject differed between treatment groups, results of the incidence rate analyses should be interpreted with caution.

The majority of the subjects in the Raptiva database received either 1.0 mg/kg/wk or 2.0 mg/kg/wk. In a few subjects, the dose was as high as 4.0 mg/kg/wk.

Given the 1620 subjects exposed to Raptiva in the placebo-controlled period of the Phase III trials, the likelihood of observing an adverse event during a 12-week treatment period with a true incidence of 1% is almost 100% and the likelihood of observing an event with a true incidence of 0.1% is ~80%. Over all studies of Raptiva with subcutaneous exposure of 8–12 weeks, the likelihood of observing an adverse event with a true incidence of 1% or 0.1% during the treatment period for the 2,556 Raptiva-treated subjects is approximately 100% and 92%, respectively.

6.2 CLINICAL RESULTS

6.2.1 Demographics and Baseline Characteristics

The baseline demographics for subjects treated with Raptiva or placebo during the first 12 weeks in the Phase III studies were comparable (see Table 16). The high body mass index (BMI) of subjects was consistent with observations that obesity is a frequent co-morbidity with psoriasis (Stern 1995; Camisa 1998). Other common co-morbid conditions were also represented in the study cohort. Overall, 33.1% of subjects had pre-existing arthritis, 24.5% had hypertension, 10.2% had hypercholesterolemia, and 9.8% had diabetes.

Table 16

Baseline Demographics for Subjects in the Phase III, Placebo-Controlled Studies 2390, 2600, 2058, and 2059

Characteristic	Placebo (n=715)	Raptiva 1.0 mg/kg/wk (n=1,213)	Raptiva 2.0 mg/kg/wk (n=407)	Raptiva All Subjects (n=1,620)	All Subjects (n=2,335)
Age (yr)					
Mean (SD)	44.7 (120)	45.6 (12.4)	45.1 (13.0)	45.5 (12.5)	45.2 (12.4)
Median	45	45	44	45	45
Range	18–75	18–75	18–74	18–75	18–75
Age group (yr)					
18–40	260 (36.4%)	428 (35.3%)	161 (39.6%)	589 (36.4%)	849 (36.4%)
41–64	417 (58.3%)	694 (57.2%)	209 (51.4%)	903 (55.7%)	1,320 (56.5%)
≥65	38 (5.3%)	91 (7.5%)	37 (9.1%)	128 (7.9%)	166 (7.1%)
Sex					
Male	465 (66.4%)	824 (67.9%)	273 (67.1%)	1,097 (67.7%)	1,572 (67.3%)
Female	240 (33.6%)	389 (32.1%)	134 (32.9%)	523 (32.3%)	763 (32.7%)
Race/ethnicity					
White	645 (90.2%)	1,087 (89.6%)	354 (87.0%)	1,411 (89.0%)	2,086 (89.3%)
Black	18 (2.5%)	28 (2.3%)	8 (2.0%)	36 (2.2%)	54 (2.3%)
Asian or Pacific Islander	18 (2.5%)	31 (2.6%)	10 (2.5%)	41 (2.5%)	59 (2.5%)
Hispanic	26 (3.6%)	53 (4.4%)	30 (7.4%)	83 (5.1%)	109 (4.7%)
American Indian or Alaskan Native	1 (0.1%)	5 (0.4%)	1 (0.2%)	6 (0.4%)	7 (0.3%)
Other	7 (1.0%)	9 (0.7%)	4 (1.0%)	13 (0.8%)	20 (0.9%)
Weight (kg)					
Mean (SD)	93.2 (20.4)	92.8 (20.1)	93.6 (20.5)	93.0 (20.2)	93.0 (20.3)
Median	91	91	92	92	91
Range	45–159	45–160	43–144	43–160	43–160
BMI (kg/m^2), n					
Mean (SD)	31.35 (6.56)	31.25 (6.45)	31.43 (6.65)	31.29 (6.50)	31.31 (6.52)
Median	30.3	30.5	30.8	30.5	30.4
Range	14.8–60.2	17.9–58.9	18.5–53.6	17.9–58.9	14.8–60.2

For baseline psoriasis characteristics, the Raptiva and placebo-treated groups were comparable (see Table 17).

Table 17

Baseline Psoriasis Characteristics for Subjects in the Phase III, Placebo-Controlled Studies 2390, 2600, 2058, and 2059

Characteristic	Placebo (n=715)	Raptiva 1.0 mg/kg/wk (n=1,213)	Raptiva 2.0 mg/kg/wk (n=407)	All Raptiva Subjects (n=1,620)	All Subjects (n=2,335)
PASI score					
Mean (SD)	19.2 (7.6)	19.3 (7.5)	19.4 (7.9)	19.4 (7.6)	19.3 (7.6)
Median	17	17	17	17	17
Range	10–58	10–59	6–56	6–59	6–59
PASI category, n					
≤16	326 (45.6%)	524 (43.2%)	174 (42.8%)	698 (43.1%)	1,024 (43.9%)
16.1–30.0	325 (45.5%)	576 (47.3%)	197 (48.4%)	773 (47.7%)	1,098 (47.0%)
>30.0	64 (9.0%)	113 (9.3%)	36 (8.8%)	149 (9.2%)	213 (9.1%)
Prior systemic treatment, n					
Yes	490 (68.5%)	861 (71.0%)	234 (59.7%)	1,104 (68.1%)	1,594 (68.3%)
No	225 (31.5%)	352 (29.0%)	164 (40.3%)	516 (31.9%)	741 (31.7%)
Percent BSA of psoriasis					
Mean (SD)	28.3 (17)	29.0 (17)	30.2 (17)	29.3 (17)	29.0 (17)
Median	23	24	25	24	24
Range	10–90	10–98	7–94	7–94	7–98
Duration of psoriasis (yr)	(n=701)	(n=1,194)	(n=395)	(n=1,589)	(n=2,290)
Mean (SD)	18.6 (11)	18.9 (12)	17.6 (12)	18.6 (12)	18.6 (12)
Median	17	17	15	16	17
Range	0–62	0–68	1–70	0–70	0–70

6.2.2 Subject Disposition (Phase III Studies)

Rates of treatment discontinuation during the first 12 weeks of exposure in the placebo-controlled Phase III studies were low. Approximately 8% of subjects discontinued treatment during the placebo-controlled phase of the four Phase III studies, with similar discontinuation rates in the placebo-treated and Raptiva-treated groups (see Table 18).

The most common adverse events leading to discontinuation for subjects receiving Raptiva during this period were headache (9 subjects; 0.6%), psoriasis (9 subjects; 0.6%), pain (6 subjects; 0.4%), arthritis (6 subjects; 0.4%), and arthralgia (0.3%).

Table 18

Subject Disposition and Reasons for Premature Discontinuation for Subjects during the First 12 Weeks of Treatment in the Phase III, Placebo-Controlled Studies 2390, 2600, 2058, and 2059

		Raptiva			
Subject Status	Placebo (n=715)	1.0 mg/kg/wk (n=1,213)	2.0 mg/kg/wk (n=407)	All Raptiva (n=1,620)	All Subjects (n=2,335)
Discontinued FT period	60 (8.4%)	85 (7.0%)	37 (9.1%)	122 (7.5%)	182 (7.8%)
Reason for FT discontinuation, n					
Adverse event	14 (2.0%)	30 (2.5%)	14 (3.4%)	44 (2.7%)	58 (2.5%)
Subject's decision	21 (2.9%)	25 (2.1%)	10 (2.5%)	35 (2.2%)	56 (2.4%)
Lost to follow-up	13 (1.8%)	12 (1.0%)	7 (1.7%)	19 (1.2%)	32 (1.4%)
Investigator's decision	8 (1.1%)	9 (0.7%)	2 (0.5%)	11 (0.7%)	19 (0.8%)
Use of excluded treatment	3 (0.4%)	8 (0.7%)	4 (1.0%)	12 (0.7%)	15 (0.6%)
Death	1 (0.1%)	0	0	0	1 (<0.1%)
Pregnancy	0	1 (0.1%)	0	1 (0.1%)	1 (<0.1%)

FT=first 12-week treatment.

6.2.3 Drug Exposure (Phase III Studies)

During the first 12 weeks of treatment in the Phase III studies, more than 70% of the subjects received all doses of study drug, with no discernible differences between the placebo and active treatment groups (see Table 19).

Table 19

Extent of Exposure to Study Drug for Subjects during the First 12 Weeks of Treatment in the Placebo-Controlled Studies 2390, 2600, 2058, and 2059

		Raptiva		
	Placebo (n=715)	1.0 mg/kg/wk (n=1,213)	2.0 mg/kg/wk (n=407)	All Raptiva Subjects (n=1,620)
Number of doses received				
Mean (SD)	11.1 (2.3)	11.3 (1.9)	11.1 (2.2)	11.2 (2.0)
Median	12	12	12	12
Subjects who received all 12 doses				
n	523 (73.1%)	902 (74.4%)	293 (72.0%)	1,195 (73.8%)
Total cumulative dose (mg)				
Mean (SD)	0	1,020.92 (285.74)	1,954.50 (612.79)	1,225.47 (565.11)
Median	0	1,015.2	1,993.1	1,123.2

6.2.4 Common Adverse Events (Phase III Studies)

Overall, 81% of all subjects had at least one adverse event during their first 12 weeks of treatment. The percentage of subjects experiencing adverse events was approximately 9% greater for the 1.0 mg/kg/wk Raptiva-treated group and 13% greater for the 2.0 mg/kg/wk Raptiva-treated group than for the placebo-treated group. All adverse events that occurred in $\geq$5% of subjects in the 1.0 mg/kg/wk group, 2.0 mg/kg/wk group, or placebo-treated group are presented in Table 20.

Table 20

Adverse Events That Occurred in ≥5% of Subjects in Any Raptiva or Placebo-Treated group during the First 12 Weeks of Treatment in the Placebo-Controlled Studies

COSTART Body System/ Preferred Term	Placebo (n=715)	Raptiva		
		1.0 mg/kg/wk (n=1,213)	2.0 mg/kg/wk (n=407)	All Raptiva Subjects (n=1,620)
Total [a]	526 (73.6%)	1,000 (82.4%)	354 (87.0%)	1,354 (83.6%)
Body as a whole				
Headache	**159 (22.2%)**	**391 (32.2%)**	**151 (37.1%)**	**542 (33.5%)**
Infection NOS	*110 (15.4%)*	*166 (13.7%)*	*59 (14.5%)*	*225 (13.9%)*
Chills	**32 (4.5%)**	**154 (12.7%)**	**53 (13.0%)**	**207 (12.8%)**
Pain	**38 (5.3%)**	**122 (10.1%)**	**45 (11.1%)**	**167 (10.3%)**
Fever	**24 (3.4%)**	**80 (6.6%)**	**46 (11.3%)**	**126 (7.8%)**
Asthenia	**37 (5.2%)**	**81 (6.7%)**	**38 (9.3%)**	**119 (7.3%)**
Flu syndrome	**29 (4.1%)**	**83 (6.8%)**	**19 (4.7%)**	**102 (6.3%)**
Accidental injury	45 (6.3%)	68 (5.6%)	27 (6.6%)	95 (5.9%)
Back pain	**14 (2.0%)**	**50 (4.1%)**	**25 (6.1%)**	**75 (4.6%)**
Digestive				
Nausea	**51 (7.1%)**	**128 (10.6%)**	**56 (13.8%)**	**184 (11.4%)**
Diarrhea	48 (6.7%)	72 (5.9%)	30 (7.4%)	102 (6.3%)
Musculoskeletal				
Myalgia	**35 (4.9%)**	**102 (8.4%)**	**32 (7.9%)**	**134 (8.3%)**
Respiratory				
Pharyngitis	47 (6.6%)	88 (7.3%)	31 (7.6%)	119 (7.3%)
Rhinitis	46 (6.4%)	81 (6.7%)	17 (4.2%)	98 (6.0%)
Sinusitis	34 (4.8%)	63 (5.2%)	14 (3.4%)	77 (4.8%)
Skin/appendages				
Herpes simplex	24 (3.4%)	49 (4.0%)	25 (6.1%)	74 (4.6%)

NOS=Not otherwise specified; this includes mostly reports of upper respiratory tract infection, with some additional events of infected psoriatic lesions, leg wound infection, and dental infection.

Note: Adverse events that occurred at rates ≥1% higher in the 1.0 mg/kg/wk Raptiva-treated group than in the placebo-treated group are indicated in bold font. Adverse events that occurred at rates ≥1% higher in the placebo-treated group than in the 1.0 mg/kg/wk Raptiva-treated group are in italics.

[a] Represents the number of subjects with at least one adverse event.

Headache, chills, fever, nausea, vomiting, and myalgia occurring within 48 hours of any dose of study drug were pre-specified as acute adverse reactions. These tended to be mild and self-limited, and are discussed in greater detail in Section 6.2.6.

Pain was reported for nearly twice as many subjects in the 1.0 mg/kg/wk Raptiva-treated group as in the placebo-treated group. Frequent descriptions of the pain were generalized body aches or pain, pain in the lower extremities (knees, ankles, feet) and dental pain. Most reports of pain were mild to moderate in intensity, with $<1\%$ reported as severe. None were serious. Only 0.4% of patients discontinued treatment because of an adverse event of pain. In addition to the 1,620 subjects who were first exposed to Raptiva in a placebo-controlled study, 954 were first exposed in an uncontrolled setting. The overall percentage of subjects with at least one adverse event and the types and rates of adverse events reported were similar in these two groups of subjects.

Common adverse events during prolonged treatment, retreatment, and drug withdrawal are presented in Sections 6.4, 6.5, and 6.6, respectively.

6.2.5 Drug-Related Adverse Events (Phase III Studies)

During the first 12 weeks of treatment in the placebo-controlled studies, investigators reported more adverse events as drug-related in subjects receiving Raptiva than in those receiving placebo. The most common types of adverse events judged to be study drug–related were headache, chills, fever, flu syndrome, nausea, and myalgia. Each of these were reported for 2%–12% more Raptiva-treated subjects than placebo-treated subjects (see Table 21). Of note, headache, chills, fever, nausea, vomiting, and myalgia were pre-specified in the protocols as potential mild to moderate adverse events associated with initial injections of Raptiva (acute adverse reactions, see Section 6.2.6).

Table 21

Study Drug–Related Adverse Events That Occurred in ≥5% of Subjects in Any Raptiva or Placebo-Treated group during the First 12 Weeks of Treatment in the Placebo-Controlled Studies

		Raptiva		
Preferred Term	Placebo (n=715)	1.0 mg/kg/wk (n=1,213)	2.0 mg/kg/wk (n=407)	All Raptiva Subjects (n=1,620)
Total [a]	217 (30.3%)	554 (45.7%)	222 (54.5%)	776 (47.9%)
Headache	96 (13.4%)	262 (21.6%)	105 (25.8%)	367 (22.7%)
Chills	19 (2.7%)	136 (11.2%)	47 (11.5%)	183 (11.3%)
Nausea	34 (4.8%)	89 (7.3%)	43 (10.6%)	132 (8.1%)
Fever	11 (1.5%)	54 (4.5%)	32 (7.9%)	86 (5.3%)
Myalgia	24 (3.4%)	70 (5.8%)	25 (6.1%)	95 (5.9%)
Asthenia	29 (4.1%)	48 (4.0%)	31 (7.6%)	79 (4.9%)

[a] Represents the number of subjects with at least one adverse event reported by the investigator as drug related.

6.2.6 Acute Adverse Reactions (Phase III Studies)

Acute adverse reactions were pre-defined as headache, fever, chills, nausea, vomiting, or myalgia starting within 48 hours (day of or two days following) of an injection of study drug. Acute reactions such as these are not uncommon with biologic agents, especially monoclonal antibodies, and generally tend to occur after the initial doses and to be mild and self-limited.

During the first 12 weeks of the placebo-controlled studies, the percentage of subjects experiencing at least one acute adverse reaction was approximately twice as great for Raptiva-treated subjects than for placebo-treated subjects. Headache was the most prevalent type of acute adverse reaction (see Table 22). The incidence of vomiting was comparable in the placebo-treated and 1.0 mg/kg/wk Raptiva-treated groups.

These events were mostly mild to moderate in intensity, and none were serious. The rate of study discontinuation due to an acute adverse reaction was less than 1%. The median duration of the events were 1–2 days, and most events were self-limited or resolved with Tylenol or NSAIDS.

Table 22

Acute Adverse Reactions Experienced by Subjects
during the First 12 Weeks of Treatment in the Placebo-Controlled Studies

		Raptiva		
Adverse Event	Placebo (n=715)	1.0 mg/kg/wk (n=1,213)	2.0 mg/kg/wk (n=407)	All Raptiva Subjects (n=1,620)
Total [a]	173 (24.2%)	485 (40.0%)	187 (45.9%)	672 (41.5%)
Headache	121 (16.9%)	341 (28.1%)	130 (31.9%)	471 (29.1%)
Chills	25 (3.5%)	142 (11.7%)	47 (11.5%)	189 (11.7%)
Nausea	42 (5.9%)	105 (8.7%)	49 (12.0%)	154 (9.5%)
Fever [b]	12 (1.7%)	61 (5.0%)	39 (9.6%)	100 (6.2%)
Myalgia	28 (3.9%)	86 (7.1%)	29 (7.1%)	115 (7.1%)
Vomiting	5 (0.7%)	13 (1.1%)	11 (2.7%)	24 (1.5%)

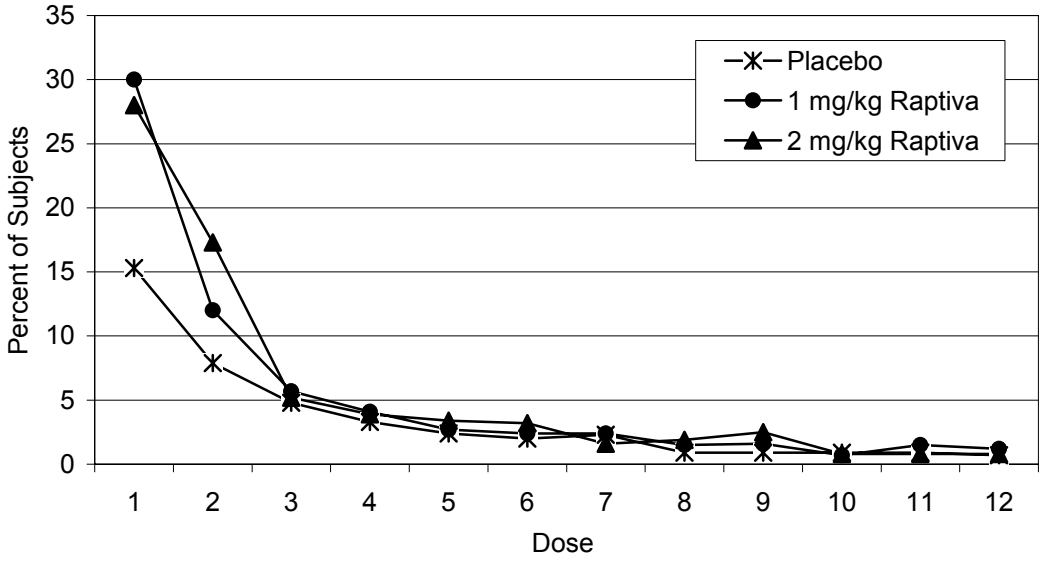
[a] Represents the number of subjects with at least one acute adverse reaction.

[b] Included subjective sensations of feverishness or warmth, rather than objectively measured temperature elevations.

The percentage of Raptiva-treated subjects with at least one acute adverse reaction was greatest with the first dose, decreased to less than half the rate with the second dose, and diminished to a percentage comparable to that for subjects treated with placebo following the third and subsequent doses (see Figure 12).

Figure 12

Acute Adverse Reactions Experienced by Subjects during the First 12 Weeks of Treatment in the Placebo-Controlled Studies



6.2.7 Deaths and Other Serious Adverse Events

a. Deaths (All Studies)

In the total psoriasis safety database, death was an infrequent and was reported for 7 of the 2762 Raptiva-treated subjects (0.3%) and 3 of the 715 placebo-treated subjects (0.4%). Two subjects died while receiving Raptiva, and 5 died after completing treatment. No deaths were attributed to study drug by the investigators. Table 23 summarizes these events.

Table 23

Deaths

Subject/ Study	Age (yr)/ Sex	Most Recent Dose	Duration of Study Drug Exposure	Time since Last Dose	Cause of Death	Clinically Relevant Medical History
11520/ 2058	60/M	1.0 mg/kg	12 Weeks	26.9 Weeks	Metastatic rectal cancer	None
68812/[c] 2059	56/M	1.0 mg/kg	12 Weeks	~72 Weeks	Accidental death (plane crash)	None
81235/ 2059	70/M	Placebo	0	9.3 Weeks	Accidental death (drowning)	Hypertension
81601/ 2059	58/M	4.0 mg/kg	9 Weeks	5 Days	Arteriosclerosis	Type 2 diabetes mellitus, hypertension, hypercholesterolemia, double coronary bypass (two procedures), intermittent bilateral leg swelling, anemia
12062/ 2062	68/F	1.0 mg/kg	20 Weeks	~38 Weeks	Unknown	Hypertension, hypercholesterolemia, diabetes, stroke, congestive heart failure, pleural disorder
17907/ 2062	68/F	1.0 mg/kg	12 Weeks	~41 Weeks	Atherosclerotic cardiovascular disease	Dyspnea, palpitations, angina, diabetes, hypertension, claudication right calf, chronic anemia
28913/ 2243	68/M	2.0 mg/kg	11 Weeks	~27 Weeks	Micronodular cirrhosis	Migraines, hypertension, hyperlipidemia, triple coronary bypass (two events), and elevated SGOT and total and direct bilirubin
41011/ 2600	53/F	Placebo	7 Days	25 Days	Sudden cardiac death	COPD
42208/ 2600	47/F	Placebo	7 Days	4 Days	Seizure	Seizures and bipolar disorder
33007/ 2391	52/M	1.0 mg/kg	161 Days	48 Days	Myocardial infarction	Hypertension and smoking

COPD = chronic obstructive pulmonary disease; F = female; M = male.

b. Serious Adverse Events

First Treatment Period of the Phase III, Placebo-Controlled Studies

In the first 12-week treatment period of the placebo-controlled studies, the percentage of subjects reporting at least one serious adverse event was low in all treatment groups. Most types of serious adverse events were reported for a single subject, and no pattern suggestive of particular toxicity was apparent. All serious adverse events reported during this period are presented in Table 24.

Table 24

Serious Adverse Events That Occurred during the First 12 Weeks of Treatment in the Placebo-Controlled Studies

		Raptiva		
Preferred Term	Placebo (n=715)	1.0 mg/kg/wk (n=1,213)	2.0 mg/kg/wk (n=407)	All Raptiva Subjects (n=1,620)
Total [a]	12 (1.7%)	24 (2.0%)	12 (2.9%)	36 (2.2%)
Cellulitis	0	1 (<0.1%)	2 (0.5%)	3 (0.2%)
Kidney calculus	0	2 (0.2%)	1 (0.2%)	3 (0.2%)
Accidental injury	0	1 (<0.1%)	1 (0.2%)	2 (0.1%)
Atrial fibrillation	0	1 (<0.1%)	1 (0.2%)	2 (0.1%)
Coronary artery disorder	0	1 (<0.1%)	1 (0.2%)	2 (0.1%)
Gastroenteritis	1 (0.1%)	1 (<0.1%)	1 (0.2%)	2 (0.1%)
Pneumonia	0	2 (0.2%)	0	2 (0.1%)
Skin carcinoma	1 (0.1%)	2 (0.2%)	0	2 (0.1%)
Chest pain	1 (0.1%)	0	1 (0.2%)	1 (<0.1%)
Fever	0	1 (<0.1%)	0	1 (<0.1%)
Headache	0	1 (<0.1%)	0	1 (<0.1%)
Sarcoidosis	0	1 (<0.1%)	0	1 (<0.1%)
Sepsis	0	1 (<0.1%)	0	1 (<0.1%)
Arteriospasm	0	1 (<0.1%)	0	1 (<0.1%)
Congestive heart failure	0	1 (<0.1%)	0	1 (<0.1%)

[a] Represents the number of subjects with at least one serious adverse event.

Table 24 (cont'd)

Serious Adverse Events That Occurred during the First 12 Weeks of Treatment in the Placebo-Controlled Studies

		Raptiva		
Preferred Term	Placebo (n=715)	1.0 mg/kg/wk (n=1,213)	2.0 mg/kg/wk (n=407)	All Raptiva Subjects (n=1,620)
Myocardial infarct	1 (0.1%)	1 (<0.1%)	0	1 (<0.1%)
Cholecystitis	0	1 (<0.1%)	0	1 (<0.1%)
Sialadenitis	0	0	1 (0.2%)	1 (<0.1%)
Diabetes mellitus	0	1 (<0.1%)	0	1 (<0.1%)
Lymphadenopathy	0	1 (<0.1%)	0	1 (<0.1%)
Bone disorder	1 (0.1%)	0	1 (0.2%)	1 (<0.1%)
Convulsion	0	0	1 (0.2%)	1 (<0.1%)
Depression	2 (0.3%)	1 (<0.1%)	0	1 (<0.1%)
Myelitis	0	1 (<0.1%)	0	1 (<0.1%)
Asthma	1 (0.1%)	0	1 (0.2%)	1 (<0.1%)
Bronchiolitis	0	1 (<0.1%)	0	1 (<0.1%)
Laryngismus	0	0	1 (0.2%)	1 (<0.1%)
Abortion	0	1 (<0.1%)	0	1 (<0.1%)
Cholelithiasis	1 (0.1%)	0	0	0
Gastrointestinal carcinoma	1 (0.1%)	0	0	0
Grand mal convulsion	1 (0.1%)	0	0	0
Lung disorder	1 (0.1%)	0	0	0

[a] Represents the number of subjects with at least one serious adverse event.

Serious adverse events occurring during more prolonged treatment, the second course of treatment, or washout are discussed in Sections 6.4, 6.5, and 6.6, respectively.

6.2.8 Malignancies (All Psoriasis Studies)

Because increased rate of malignancies have been seen with other immunosuppressive agents used to treat psoriasis, malignancy data from the Raptiva clinical program was closely examined.

During the initial 12-week treatment period of the randomized, placebo-controlled, Phase III studies, malignancies were reported for 2 subjects receiving placebo (0.3%; one event each of gastrointestinal carcinoma and non-melanomatous skin cancer [NMSC]) and 4 subjects receiving Raptiva (0.2%; four events of NMSC). Across all clinical studies of Raptiva in psoriasis, the observed incidence rate of malignancy in Raptiva-treated subjects was similar to that observed in placebo-treated subjects (see Table 25).

Table 25

Incidence Rates for Malignancies in the Psoriasis Clinical Trials

Type of Malignancy	Treatment	Observed No. of Subjects	Observed Subject-Years	Rate/ 100 Subject-Years	95% CI for Rate
All	Placebo	3	185.44	1.62	0.33, 4.73
	Raptiva	30	1,782.43	1.68	1.14, 2.40
Solid tumor	Placebo	1	185.69	0.54	0.01, 3.00
	Raptiva	8	1,790.06	0.45	0.19, 0.88
NMSC	Placebo	2	185.51	1.08	0.13, 3.89
	Raptiva	20	1,784.15	1.12	0.68, 1.73
Lymphoma [a]	Placebo	0	185.69	0	0, 1.99
	Raptiva	1	1,790.90	0.06	0.00, 0.31
Malignant melanoma	Placebo	0	185.69	0	0, 1.99
	Raptiva	1	1,790.82	0.06	0.00, 0.31

NMSC = non-melanomatous skin cancer.

Note: Includes data from psoriasis studies HU9602, HUPS249, HUPS252, HUPS254, HUPS256, 2058, 2059, 2062, 2142, 2243, 2390, 2391, and 2600.

The individual numbers may not add up to the total because some patients had more than one malignancy. The subject-years vary slightly due to censoring of the subjects after their malignancy.

[a] No case of lymphoproliferative disease was seen; one case of Hodgkin's lymphoma was seen.

The eight solid tumors in Raptiva-treated patients consisted of four cases of gastrointestinal carcinoma, two of prostatic carcinoma, and one each of breast carcinoma and lung carcinoma.

NMSC includes both squamous cell and basal cell skin cancers. For 20 Raptiva-treated subjects, there were 13 reports of basal cell and 13 reports of squamous cell cancer. For 2 placebo-treated subjects, there

were two reports each of basal cell and squamous cell cancers. Thus, for both Raptiva-treated and placebo-treated subjects, the ratio of basal cell to squamous cell lesions was 1:1.

At the time of the submission of the Safety Update, there was one reported case of Hodgkin's lymphoma, which is generally not associated with immunosuppression (see Table 25). There had been no reported cases of lymphoproliferative disease during the formal study follow-up period, although one case of cutaneous T-cell lymphoma, which occurred 28 weeks after the last dose of Raptiva, had been reported. Since this submission, a B-cell lymphoma case was reported in a subject participating in an ongoing study. This additional case of lymphoma, along with an updated estimate for subject-years of observation (2203.16 subject-years), yields an incidence rate of 0.09 per 100 subject-years and a 95% confidence interval of 0.01 and 0.33, which is consistent with the expected background rate.

Because of the disparity in observation time for subjects receiving Raptiva or placebo, and given the low incidence of malignancies, the comparison between placebo and Raptiva must be made with caution. Therefore, the observed frequency of malignancy in Raptiva-treated subjects was also compared with expected frequencies derived from up to three external reference cohorts. These external cohorts were the U.S. general population (age- and sex-adjusted rates from the Surveillance, Epidemiology and End Results [SEER] database, the national tumor registry) and two moderate to severe psoriasis cohorts identified from insurance claims databases: UnitedHealthcare and Saskatchewan Health.

At the time of the submission of the Safety Update, the observed numbers of Raptiva-treated subjects with lymphoma, solid tumors, or malignant melanomas were consistent with the number of expected cases estimated from the reference cohort data (see Table 26). With the additional B-cell lymphomas, the observed two cases of lymphoma (one Hodgkin's lymphoma and one non-Hodgkin's lymphoma) in Raptiva-treated subjects remained within the expected range based on data from two external cohorts (Saskatchewan Health: 3.7 and UnitedHealthcare: 2.9) using updated subject-years of observation. The published literature indicates that moderate to severe plaque psoriasis patients are at an increased risk of

lymphoproliferative disorder compared with the general population (Margolis et al. 2001).

The observed number of cases of NMSCs in Raptiva-treated subjects was greater than the expected number based on the Saskatchewan and UnitedHealthcare cohorts. This difference between the observed and expected cases may represent ascertainment bias, since subjects in the Raptiva clinical trials were subject to more intensive surveillance, particularly of dermatologic lesions, than patients receiving standard clinical care. Ascertainment bias for skin cancer among in psoriasis study cohorts has been reported in the literature (Marcil and Stern 2001).

Table 26

Observed versus Expected Rates of Malignancies: Raptiva-Treated Subjects

	Raptiva-Treated Subjects			External Reference Cohorts		
Malignancy Category	Observed No. of Subjects	95% Confidence Interval	Observed Subject-Years	Cohort	Expected No. of Patients [a]	95% Confidence Interval
Solid tumor	8	3.45, 15.76	1,790.06	SH	7.3	4.3, 11.6
				UHC	4.7	2.3, 8.1
				SEER	7.8	NA
NMSC [b]	20	12.22, 30.89	1,784.15	SH	7.0	3.9, 11.2
				UHC	7.0	4.1, 11.1
Lymphoma	1	0.03, 5.57	1,790.90	SH	3.0	1.3, 6.3
				UHC	2.3	0.9, 5.0
				SEER	0.6	NA
Malignant melanoma [c]	1	0.03, 5.57	1,790.82	SH	0.4	0.0, 2.3
				SEER	0.4	NA

NA = not available; NMSC = non-melanomatous skin cancer; SEER = Surveillance, Epidemiology and End Results; SH = Saskatchewan Health; UHC = UnitedHealthcare.

[a] Calculation of the expected number of events was based on the expected rate of events per 100 patient-years multiplied by the observed number of subject-years in the psoriasis Raptiva trials divided by 100. The unadjusted expected incidence rates and number of events were given for the SH and UHC databases, whereas those derived from the SEER database were age and sex adjusted.

[b] SEER does not compile incidence rates for NMSC.

[c] UHC did not provide estimates for malignant melanoma.

6.2.9 Infection-Related Adverse Events (Phase III Studies)

Infections can also be increased with immunosuppressive agents, and the infection data from the Raptiva program was also examined very closely.

During the 12-week treatment period of the placebo-controlled studies, the occurrence of diagnosed infections was comparable between Raptiva- and placebo-treated subjects (see Table 27). Seven subjects who received Raptiva experienced eight serious adverse events of infection. The events were cellulitis (three events reported), pneumonia (two events), gastroenteritis (two events), and sepsis (one event). One placebo-treated subject experienced a serious adverse event of gastroenteritis.

During the first exposure to Raptiva in the open-label studies, the percentage of subjects with at least one diagnosed infection and the types of infections were similar to those for subjects receiving Raptiva in the placebo-controlled studies.

Table 27

Adverse Events Diagnostic of Infection That Occurred
during the First 12 Weeks of Treatment in the Placebo-Controlled Studies

Preferred Term	Placebo (n=715)	Raptiva 1.0 mg/kg/wk (n=1,213)	Raptiva 2.0 mg/kg/wk (n=407)	Raptiva All Raptiva Subjects (n=1,620)
Total [a]	188 (26.3%)	350 (28.9%)	114 (28.0%)	464 (28.6%)
Infection NOS	110 (15.4%)	166 (13.7%)	59 (14.5%)	225 (13.9%)
Herpes simplex [b]	24 (3.4%)	49 (4.0%)	25 (6.1%)	74 (4.6%)
Gastroenteritis	24 (3.4%)	29 (2.4%)	5 (1.2%)	34 (2.1%)
Bronchitis	9 (1.3%)	27 (2.2%)	4 (1.0%)	31 (1.9%)
Viral infection	8 (1.1%)	27 (2.2%)	3 (0.7%)	30 (1.9%)
Urinary tract infection	9 (1.3%)	19 (1.6%)	8 (2.0%)	27 (1.7%)
Otitis media	9 (1.3%)	18 (1.5%)	5 (1.2%)	23 (1.4%)
Infection, bacterial	4 (0.6%)	15 (1.2%)	4 (1.0%)	19 (1.2%)
Fungal dermatitis	1 (0.1%)	5 (0.4%)	9 (2.2%)	14 (0.9%)
Cellulitis	3 (0.4%)	9 (0.7%)	4 (1.0%)	13 (0.8%)
Periodontal abscess	2 (0.3%)	8 (0.7%)	1 (0.2%)	9 (0.6%)
Infection, fungal	0	6 (0.5%)	1 (0.2%)	7 (0.4%)
Pneumonia	2 (0.3%)	7 (0.6%)	0	7 (0.4%)
Furunculosis	3 (0.4%)	4 (0.3%)	3 (0.7%)	7 (0.4%)
Herpes zoster [b]	0	4 (0.3%)	0	4 (0.2%)
Abscess	0	3 (0.2%)	0	3 (0.2%)
Vaginal moniliasis	1 (0.1%)	3 (0.2%)	0	3 (0.2%)
Infection, parasitic	0	1 (<0.1%)	1 (0.2%)	2 (0.1%)
Oral moniliasis	0	2 (0.2%)	0	2 (0.1%)
Axillary moniliasis	0	1 (<0.1%)	0	1 (<0.1%)
Sepsis	0	1 (<0.1%)	0	1 (<0.1%)
Hepatitis	0	0	1 (0.2%)	1 (<0.1%)
Meningitis	0	0	1 (0.2%)	1 (<0.1%)
Moniliasis	1 (0.1%)	0	0	0

NOS = not otherwise specified; includes mostly reports of upper respiratory tract infection, with some additional events of infected psoriatic lesions, leg wound infection, and dental infection.

[a] Represents the number of subjects with at least adverse event diagnostic of infection.

[b] No events of systemic herpes simplex or zoster were reported.

a. Integrated Analysis of Serious Infections Requiring Hospitalization (All SC Psoriasis Studies Conducted by Genentech)

The rate of infections leading to hospital admission was slightly higher in the subjects receiving Raptiva compared with the subjects receiving placebo. However, the difference was small, and the confidence intervals overlapped. Given the low frequency, and given that the placebo rate is based on two incidents, the rates must be interpreted with caution. The rates seen in both groups are comparable to the expected number based on a Saskatchewan Health (SH) claims database for patients with psoriasis (see Table 28).

Table 28

Observed versus Expected Infections Requiring Hospitalization

Treatment	Observed No. of Subjects with Events	Observed Subject-Years	Observed Incidence Rate/100 Patient-Years	95% Confidence Interval	Expected No. of Patients with Events [a]	95% Confidence Interval
Placebo	2	169.48	1.18	0.14, 4.26	3.1	2.4, 3.8
Raptiva	27	1,680.67	1.61	1.06, 2.34	30.3	23.7, 38.2

[a] The expected number of events was calculated as the expected rate of events per 100 patient-years in the Saskatchewan Health cohort multiplied by the observed number of subject-years in the psoriasis Raptiva trials divided by 100.

b. Opportunistic Infections

An examination of the entire safety database for Raptiva revealed only one infection potentially representative of an opportunistic infection. One subject developed *Legionella* pneumonia 6 weeks after the last dose of Raptiva. Of note, *Legionella* was diagnosed contemporaneously in at least 2 other individuals (not taking Raptiva) within the same geographic area as the study subject. The Raptiva subject was not the index case. There were no cases of tuberculosis, toxoplasmosis, histoplasmosis, or other opportunistic infections observed during the Raptiva program.

6.2.10 Thrombocytopenia (All Psoriasis Studies)

To date, eight occurrences of NCI-CTC Grade 3 TCP (platelet count < 50 K/mm^3), Grade 4 TCP (platelet count < 10 K/mm^3), or TCP that was

classified as “serious” by investigators have been reported over all completed and ongoing Raptiva psoriasis studies.

An independent medical platelet expert reviewed the eight cases to assess the likelihood of a causal or contributory relationship to Raptiva exposure. One occurrence of NCI-CTC Grade 3 TCP was considered to be related to prostate cancer (Subject No. 23512), and a second case was in a subject who had been previously diagnosed with idiopathic thrombocytopenic purpura (Subject No. 2523900259). The remaining six cases were judged to have characteristics consistent with possible drug-induced TCP. These cases are summarized in Table 29.

Table 29

NCI-CTC Grade 3 or 4 Thrombocytopenia Events or Thrombocytopenia Occurrences Classified by the Investigators as Serious

Subject/ Demographics	Study	Raptiva Dose(s) (mg/kg/wk)	Platelet Nadir Count $\times 10^3/mm^3$	Weeks from First Raptiva Dose to Platelet Nadir	Clinical Signs and Symptoms
10501/ 61-yr-old White male	2058	2.0	52	18	None
27103/ 29-yr-old White male	2243	1.0–2.0	28	71	None
33203/ 41-yr-old White female	2391	1.0	10	13	Vaginal bleeding, abdominal ecchymosis
37204/ 78-yr-old White female	2601	1.0	27	14	None
41232/ 39-yr-old White male	2601	1.0	16	24	Blood in stool
44202/ 73-yr-old White female	2601	1.0	3	20	Bleeding with scratching: petechiae

Note: The two cases of Grade 3 TCP that were judged to be related to prostate cancer and ITP are not included in this table. Some cases of TCP were reported after the BLA submission.

In 5 subjects, the platelet nadir occurred between 13 and 24 weeks after the first dose of Raptiva. Based on available platelet count measurements, the onset of the platelet decline appeared to occur between 8 and 12 weeks after the first dose of Raptiva. All 6 subjects discontinued Raptiva and their platelet counts recovered rapidly. Five subjects were treated with systemic corticosteroids, and 1 also received Rh immune globulin and a platelet transfusion. Bone marrow aspirates and biopsies in 2 subjects showed no evidence of bone marrow suppression. The 6 subjects have not tested positive for anti-Raptiva antibodies. The clinical course and rapid response to corticosteroids are consistent with immune-mediated TCP. No subject had evidence of disseminated intravascular coagulation or thrombotic events.

Four subjects who developed NCI-CTC Grade 3 or 4 TCP during Raptiva treatment had received other medications or had concurrent medical conditions that could have contributed or predisposed the subject to the onset of TCP. One subject each had been started on valproic acid and cephalexin just prior to the onset of TCP. According to the Package Inserts, these two drugs have been associated with TCP. Other potential contributing conditions were viral illnesses in 3 subjects and Grave's disease in 2 others.

The incidence of TCP during the first 12 weeks of treatment in the four placebo-controlled studies (2058, 2059, 2390, and 2600) is summarized in Table 30. TCP was conservatively defined as any platelet count below 130 K/mm^3 (the lower limit of laboratory normal range) during the first 12 weeks of treatment regardless of baseline count. Overall, 21 Raptiva-treated subjects (1.3%) and 2 placebo-treated subjects (0.3%) experienced platelet counts below 130 K/mm^3 during the FT period. Because 9 of the 21 Raptiva-treated subjects had baseline platelet counts $<$130 K/mm^3, only 12 Raptiva-treated subjects (0.7%) experienced treatment-emergent platelet counts $<$130 K/mm^3 during the FT period, compared with 2 (0.3%) placebo-treated subjects.

Table 30

Thrombocytopenia during the First 12 Weeks of Treatment in the Placebo-Controlled Studies

Lowest Platelet Count ($\times 10^3/mm^3$)	Placebo (n=715)	Raptiva		
		1.0 mg/kg/wk (n=1,213)	2.0 mg/kg/wk (n=407)	All Raptiva Subjects (n=1,620)
Any count $<130/mm^3$	2 (0.3%)	13 (1.1%)	8 (2.0%)	21 (1.3%)
100 to $<130/mm^3$	1 (0.1%)	11 (0.9%)	4 (1.0 %)	15 (0.9%)
75 to $<100/mm^3$	1 (0.1%)	2 (0.2%)	3 (0.7%)	5 (0.3%)
50 to $<75/mm^3$	0	0	0	0
25 to $<50/mm^3$	0	0	1 (0.2%)	1 (0.1%)
$<25/mm^3$	0	0	0	0

Analyses of the incidence of platelet counts of <130 K/mm^3 during first exposure and extended exposure periods (through 72 weeks) from all completed studies showed no evidence for an increasing risk of TCP with extended Raptiva exposure beyond 24 weeks.

The incidence of treatment-emergent TCP was summarized for all completed and ongoing Raptiva studies based on the data used for the Safety Update to the original BLA. (Note: This excludes three cases in Table 34 from ongoing Study 2601). Treatment-emergent TCP was defined as a shift in platelet counts from normal or high values at baseline (≥ 130 K/mm^3) to below 130 K/mm^3 or shift from low at baseline (<130 K/mm^3) to $<75\%$ of baseline count. Among subjects receiving Raptiva or who were previously treated with Raptiva, there were 44 cases of treatment-emergent TCP reported over 1,668 subject-years of observation, giving an incidence rate of 2.64 events per 100 subject-years. Among subjects receiving placebo with no prior Raptiva exposure, there were two cases of treatment-emergent TCP reported over 169 subject-years of observation, giving an incidence rate of 1.18 events per 100 subject-years. The ratio of incidence rates (Raptiva to placebo) for treatment-emergent TCP was 2.24.

6.2.11 Adverse Events of Psoriasis (Phase III Studies)

a. Psoriasis Adverse Events during Treatment (Phase III Studies)

No subject experienced a serious adverse event of psoriasis during the first 12-week treatment period of the placebo-controlled studies. The overall incidence of non-serious psoriatic adverse events was low (3.2% in each dose group) in subjects receiving Raptiva; the rate was 1.4% in the placebo-treated group. Guttate psoriasis was the predominant type of psoriatic adverse event. The incidence of severe psoriasis adverse events was also low: 0.7% in the Raptiva-treated group and 0% in the placebo-treated group. The rates of study drug discontinuation because of an adverse event of psoriasis were 0.6% and 0.1% in the Raptiva and placebo-treated groups, respectively.

b. Adverse Events of Psoriasis during Washout

Use of other psoriasis therapies was restricted after Raptiva discontinuation in the clinical trials. In the early trials, psoriasis treatments were discouraged even after relapse (loss of 50% of previous improvement during Raptiva treatment). Although appropriate in the setting of a clinical trial, this approach is not consistent with clinical practice. In later studies, subjects were allowed to transition to topical treatments or UVB after Raptiva discontinuation and were also allowed to use systemic therapies or PUVA after relapse.

Across all studies (controlled and open-label), adverse events of psoriasis during Washout (the 12-week period following discontinuation of Raptiva) were reported by 13.0% of subjects who completed the Adverse Event Form (see Table 31).

Table 31

Psoriasis Adverse Events Experienced by Subjects Previously Treated with Raptiva during Washout

Adverse Event	Raptiva (n = 1,201)
Subjects with completed forms	1,166
Total [a]	152 (13.0%)
Recurrence of plaque psoriasis	73 (6.3%)
Unusual morphology	42 (3.6%)
Guttate psoriasis	24 (2.1%)
Psoriatic erythroderma [c]	8 (0.7%)
Pustular psoriasis [b]	7 (0.6%)
Inverse psoriasis	2 (0.2%)

[a] The total represents the number of subjects with completed Adverse Event Case Report Forms.

[b] One case of pustular psoriasis of von Zumbusch, five localized with pustular lesions restricted to the groin, palms, or soles.

[c] Erythrodermic flare and psoriatic erythroderma.

Only 6 subjects (0.5% of 1,166 subjects) had adverse events of psoriasis that were reported as serious: psoriatic erythroderma (3 subjects), pustular psoriasis (2 subjects), and recurrence of plaque psoriasis (1 subject) (see Table 32). Of note, 3 of the subjects received the 4.0 mg/kg/wk dose and 1 received the 2.0 mg/kg/wk dose. Five of the subjects were admitted to the hospital for management. At the termination of Raptiva treatment, 2 of the 6 subjects were responders and 4 were non-responders.

Subjects who transitioned to topical therapies or UVB after Raptiva discontinuation or started systemic therapies after relapse experienced lower rates of psoriatic adverse events than did untreated patients (see Table 32). therapeutics.

Table 32

Psoriasis Adverse Events by Medication Received during Washout for Evaluable Subjects from Studies HUPS254, HUPS256, 2058, 2059, 2142, 2243, and 2062

Subject Group	No. of Subjects Experiencing a Psoriasis Adverse Event [a]
Total	152/1,166 (13.0%)
No psoriasis therapy	96/458 (21.0%)
Topical therapies	53/627 (8.5%)
Phototherapies	7/116 (6.0%)
Systemic therapies	9/262 (3.4%)

[a] Subjects who washed out and had completed CRFs for both adverse events and concomitant medications.

Rates of more clinically significant psoriasis adverse events, defined as psoriasis adverse events excluding mild and guttate-type lesions, were reduced to 0.5% in subjects receiving high-potency topical corticosteroids and to 0.0% in subjects receiving topical vitamin D derivatives (see Table 33).

Table 33

Rate of Adverse Events of Psoriasis, Excluding Mild and Guttate Psoriasis, by Concomitant Therapy during Washout

Treatment	Rate of Psoriasis Adverse Events
No psoriasis medication	13.3% (65/489)
Medium-potency corticosteroids	3.7% (11/297)
High-potency corticosteroids	0.5% (1/186)
Vitamin D derivatives	0 (0/105)
Ultraviolet light B	2.7% (2/74)
Systemic retinoids	0 (0/24)
Methotrexate	1.2% (1/81)
Cyclosporine	0 (0/55)

Note: Includes serious, severe, or moderate adverse events, excluding guttate psoriasis, and subjects with at least two PASI evaluations from Studies 2058, 2059, 2062, and 2142.

The incidence of psoriatic adverse events following withdrawal of Raptiva may have been increased by the clinical trial design, which restricted Raptiva taper, transition to alternate therapies, or use of concomitant medications. The above data suggest that subjects who received concomitant psoriasis medications during washout had a lower incidence of psoriasis adverse events. In clinical practice, it is anticipated that patients will be transitioned or rotated to other therapies upon discontinuation of Raptiva and that they will receive treatment with re-initiation of Raptiva or initiation of other psoriasis therapies upon recurrence of psoriasis. Additional trials are in progress assessing Raptiva taper regimens (Study 2391) and transition to other psoriasis therapies (Study HUPS300).

6.2.12 Arthritis (Phase III Studies)

During the first 12-week treatment period of the Phase III, placebo-controlled studies, the rate of arthritis in the placebo-treated group (2.2%) was similar to the rate in the 1.0 mg/kg/wk Raptiva-treated group (2.4%). The rate in the 2.0 mg/kg/wk group was similar but slightly higher (3.9%). There were no serious adverse events of arthritis during this period. The majority of subjects who reported arthritis adverse events had prior history of arthritis. In the overall database a few (0.6%) subjects experienced a serious adverse event of arthritis.

Because arthritis is not the same as psoriatic arthritis, a Phase III study to evaluate the safety and efficacy of Raptiva in psoriatic arthritis patients is ongoing.

6.2.13 Hypersensitivity-Related Adverse Events (Phase III Studies)

Hypersensitivity-related adverse events were defined as an adverse event that included a symptom such as urticaria or angioedema, which could be suggestive of a potential hypersensitivity reaction, regardless of suspected relationship to Raptiva. During the first 12-week treatment period of the four Phase III, placebo-controlled studies, the percentage of subjects reporting at least one hypersensitivity-related adverse event was similar in the placebo and 1.0 mg/kg/wk Raptiva-treated groups, and somewhat higher in the 2.0 mg/kg/wk Raptiva-treated group (see Table 34). The most frequent events were rash, urticaria, and allergic reaction. Most events of allergic reaction

were described as seasonal allergy or allergic rhinitis. Although 22 of the 1,620 subjects (1.4%) receiving Raptiva experienced urticaria; however only 2 subjects discontinued treatment. Most patients experienced resolution of the urticaria despite continued treatment and/or rechallenge. Therefore, many hypersensitivity-related adverse events did not appear related to Raptiva.

Table 34

Hypersensitivity Adverse Events That Occurred during the First 12 Weeks of Treatment in the Placebo-Controlled Studies

		Raptiva		
Adverse Event	Placebo (n=715)	1.0 mg/kg/wk (n=1,213)	2.0 mg/kg/wk (n=407)	All Raptiva Subjects (n=1,620)
Total [a]	49 (6.9%)	95 (7.8%)	37 (9.1%)	132 (8.1%)
Rash	20 (2.8%)	37 (3.1%)	11 (2.7%)	48 (3.0%)
Urticaria	3 (0.4%)	16 (1.3%)	6 (1.5%)	22 (1.4%)
Allergic reaction	6 (0.8%)	14 (1.2%)	5 (1.2%)	19 (1.2%)
Dyspnea	3 (0.4%)	9 (0.7%)	3 (0.7%)	12 (0.7%)
Face edema	6 (0.8%)	6 (0.5%)	3 (0.7%)	9 (0.6%)
Maculopapular rash	3 (0.4%)	8 (0.7%)	2 (0.5%)	10 (0.6%)
Injection-site hypersensitivity	1 (0.1%)	6 (0.5%)	2 (0.5%)	8 (0.5%)
Asthma	6 (0.8%)	4 (0.3%)	3 (0.7%)	7 (0.4%)
Angioedema	0	1 (<0.1%)	3 (0.7%)	4 (0.2%)
Laryngismus	5 (0.7%)	1 (<0.1%)	1 (0.2%)	2 (0.1%)
Bronchiolitis	0	1 (<0.1%)	0	1 (<0.1%)
Erythema multiforme	0	1 (<0.1%)	0	1 (<0.1%)

[a] Represents the number of subjects with at least one hypersensitivity adverse event.

The rate of hypersensitivity adverse events was similar between patients who were positive for anti-Raptiva antibodies and those who were negative, except during retreatment. During retreatment with Raptiva, hypersensitivity related adverse events were reported for 18.2% of antibody-positive subjects (4 of 22 subjects) compared with 6.7% of all subjects (23 of 341 subjects).

6.2.14 Injection-Site Adverse Events (Phase III Studies)

Less than 1% of subjects in the first 12-week treatment period of the Phase III, placebo-controlled studies experienced a visible adverse reaction at the injection site, with no discernible differences noted between the Raptiva and placebo-treated groups. Injection-site pain was experienced by about 1% of patients, with similar incidence in the Raptiva and placebo-treated groups.

6.2.15 Audiologic Assessments

Audiologic testing was performed in three studies (HUPS254, HUPS256, 2058) after 1 subject in the Phase II study (HUPS252) experienced a serious adverse event of transient unilateral hearing loss. In all three studies, audiograms showed improvement and worsening in similar proportions of subjects. Overall, the observations appeared to be consistent with test-retest variability without evidence of Raptiva-induced ototoxicity. Two expert audiologists who reviewed audiograms from Studies HUPS254, HUPS256, and 2058 concluded that there was no evidence of ototoxicity.

6.3 LABORATORY SAFETY TESTS (PHASE III STUDIES)

The pertinent findings from laboratory tests are summarized below:

- The most common abnormality is an approximate doubling of mean lymphocyte count that was present throughout Raptiva treatment and resolved after discontinuation; elevations of eosinophil and neutrophil counts were seen to a lesser degree.
- A small excess of treatment-emergent thrombocytopenia (TCP) events was observed among Raptiva-treated subjects compared with placebo-treated subjects. These events were rare and reversible upon discontinuation of Raptiva with or without corticosteroid administration (see Section 6.2.10 for additional details).
- Blood chemistry abnormalities more common in Raptiva-treated subjects versus placebo-treated subjects were as follows:

  1) Small increases in alkaline phosphatase (mean change [SD] of -0.68 [1.82] U/L in placebo-treated group versus 5.98 [17.43] U/L in Raptiva-treated group)

2) A small increase in the proportion of subjects with a shift to elevated alkaline phosphatase (0.6% high shifts in placebo-treated group vs. 4.1% in Raptiva-treated group)

3) A small increase in the proportion of subjects with a shift to SGPT/ALT (2.6% high shifts in placebo vs. 5.0% in Raptiva-treated groups). Fractionation demonstrated the increase in high shifts in alkaline phosphatase not to be primarily due to increases in liver isoenzymes.

- Examination of C-reactive protein (CRP) and fibrinogen as representative acute phase reactants demonstrated increases in some Raptiva-treated subjects. For CRP, 22.5% Raptiva-treated subjects experienced high shifts compared with 13.0% of placebo-treated subjects. Mean (SD) change from baseline was 0.40 (1.83) in Raptiva treated subjects compared with 0.09 (0.84) in placebo-treated subjects.
- Anti-Raptiva antibodies were detected in 67 of the 1,063 subjects (approximately 6.3%), with 0.3% of subjects having titers >1.0 μg/mL. No apparent differences were noted in safety, efficacy, and pharmacodynamic results between subjects who developed anti-Raptiva antibodies and those who did not. In subjects who were anti-Raptiva antibody positive, the PASI 75 response was 20.0% and the PASI-50 response was 53.3% after 12 weeks of treatment.

6.4 LONG-TERM CLINICAL RESULTS

Extended exposure is defined as treatment with Raptiva for two or more periods, each usually of 12 weeks duration, for which the interval between the last dose of study drug in a previous treatment period and the first dose of drug in the subsequent treatment period is $\leq$35 days. Extended exposure safety data from all studies were pooled by length of exposure in 12-week increments: 0–12 weeks (First Exposure), 12–24 weeks, 24–36 weeks, 36–48 weeks, and 48–60 weeks.

The data summarized over the first 12 weeks of treatment and used for comparison with the extended exposure segments were obtained from subjects who were eligible for extended exposure, in order to make the most appropriate comparison between the periods. As a result, first exposure data for any subject who could not have received extended exposure were not included.

For subjects who received 1.0 mg/kg/wk or 2.0 mg/kg/wk Raptiva, the percentage of subjects with at least one adverse event was higher during the first 12 weeks of treatment than in any of the subsequent extended exposure 12-week segments. Low discontinuation rates (see Table 18) preclude the possibility that the reduction in adverse events is due to preferential discontinuation of subjects experiencing adverse events.

All adverse event types that occurred in at least 5% of subjects during any 12-week treatment segment from first exposure through 60 weeks are presented in Table 35. For most types of adverse events, the percentage of subjects reporting the event was lower during every extended exposure segment than during the first 12-week treatment period. There were no noteworthy trends toward higher percentages of adverse events with longer Raptiva exposure.

Table 35

Adverse Events Experienced by ≥5% of Subjects by 12-Week Course of Raptiva Treatment

Adverse Event	Placebo [a] 0–12 Wk (n=715)	Raptiva 0–12 Wk [b] (n=1,713)	Raptiva 12–24 Wk (n=1,115)	Raptiva 24–36 Wk (n=318)	Raptiva 36–48 Wk (n=247)	Raptiva 48–60 Wk (n=228)
Total	526 (73.6%)	1,420 (82.9%)	754 (67.6%)	196 (61.6%)	143 (57.9%)	106 (46.5%)
Headache	159 (22.2%)	585 (34.2%)	78 (7.0%)	14 (4.4%)	6 (2.4%)	8 (3.5%)
Infection	110 (15.4%)	249 (14.5%)	167 (15.0%)	52 (16.4%)	33 (13.4%)	25 (11.0%)
Chills	32 (4.5%)	204 (11.9%)	12 (1.1%)	3 (0.9%)	2 (0.8%)	0
Nausea	51 (7.1%)	198 (11.6%)	31 (2.8%)	5 (1.6%)	4 (1.6%)	1 (0.4%)
Pain	38 (5.3%)	187 (10.9%)	59 (5.3%)	18 (5.7%)	11 (4.5%)	6 (2.6%)
Fever	24 (3.4%)	149 (8.7%)	20 (1.8%)	8 (2.5%)	4 (1.6%)	3 (1.3%)
Asthenia	37 (5.2%)	136 (7.9%)	21 (1.9%)	3 (0.9%)	0	2 (0.9%)
Pharyngitis	47 (6.6%)	129 (7.5%)	36 (3.2%)	12 (3.8%)	10 (4.0%)	2 (0.9%)
Myalgia	35 (4.9%)	129 (7.5%)	22 (2.0%)	3 (0.9%)	2 (0.8%)	2 (0.9%)
Diarrhea	48 (6.7%)	111 (6.5%)	38 (3.4%)	5 (1.6%)	4 (1.6%)	5 (2.2%)
Rhinitis	46 (6.4%)	103 (6.0%)	40 (3.6%)	25 (7.9%)	14 (5.7%)	3 (1.3%)
Accidental injury	45 (6.3%)	100 (5.8%)	47 (4.2%)	15 (4.7%)	7 (2.8%)	2 (0.9%)
Flu syndrome	29 (4.1%)	88 (5.1%)	32 (2.9%)	3 (0.9%)	6 (2.4%)	1 (0.4%)
Back pain	14 (2.0%)	85 (5.0%)	30 (2.7%)	8 (2.5%)	6 (2.4%)	4 (1.8%)
Cough increased	31 (4.3%)	80 (4.7%)	41 (3.7%)	14 (4.4%)	15 (6.1%)	5 (2.2%)
Sinusitis	34 (4.8%)	76 (4.4%)	34 (3.0%)	10 (3.1%)	21 (8.5%)	6 (2.6%)

[a] Placebo data from the first 12-week treatment period of the four Phase III, randomized, placebo-controlled studies.

[b] Comparisons were made with subjects treated with Raptiva from the subset of subjects eligible for continued treatment beyond the initial 12 weeks. The Raptiva-treated groups were combined.

Serious adverse events that occurred during treatment beyond 12 weeks are presented in Table 36. Based on the available data, the overall rates of serious adverse events did not increase with increased exposure to Raptiva, nor was there any evidence of cumulative toxicity over time.

Table 36

Serious Adverse Events Reported for 2 or More Subjects Treated with Raptiva within Any 12-Week Treatment Period of the Placebo-Controlled and Open-Label Studies

	Extended Exposure				
Adverse Event	FE [a] (n = 1,713)	13–24 Wk (n = 1,115)	25–36 Wk (n = 318)	37–48 Wk (n = 247)	49–60 Wk (n = 228)
Total	43 (2.5%)	28 (2.5%)	6 (1.9%)	9 (3.6%)	6 (2.6%)
Cellulitis	5 (0.3%)	2 (0.2%)	0	0	0
Arthritis	5 (0.3%)	1 (< 0.1%)	0	1 (0.4%)	0
Accidental injury	4 (0.2%)	2 (0.2%)	0	1 (0.4%)	0
Kidney calculus	3 (0.2%)	0	0	0	0
Skin carcinoma	2 (0.1%)	3 (0.3%)	0	2 (0.8%)	1 (0.4%)
Bone disorder	2 (0.1%)	0	0	0	0
Pneumonia	1 (< 0.1%)	0	0	0	0
Coronary artery disorder	2 (0.1)	1 (< 0.1%)	0	0	0
Gastroenteritis	2 (0.1%)	1 (< 0.1%)	0	0	1 (0.4%)
Bronchiolitis	1 (< 0.1%)	0	0	0	0
Atrial fibrillation	1 (< 0.1%)	0	0	0	0
Psoriasis	1 (< 0.1%)	3 (0.3%)	0	0	0
Deep vein thrombophlebitis	0	2 (0.2%)	1 (0.3%)	0	0
GI carcinoma	0	2 (0.2%)	0	0	1 (0.4%)
GI disorder	0	2 (0.2%)	0	0	0
Infection	0	0	0	0	0
Anemia	0	0	0	0	0

FE = first exposure; GI = gastrointestinal.

[a] Comparisons were made with subjects treated with Raptiva from the subset of subjects eligible for continued treatment beyond the initial 12 weeks. The Raptiva-treated groups were combined.

The long-term treatment data, based on over 1,000 subjects treated for over 24 weeks and over 200 subjects treated for over 1 year, are consistent with lack of increased toxicity with extended treatment.

6.5 RETREATMENT RESULTS

The safety of retreatment was assessed in subjects who received two 12-week treatment courses separated by a break of at least 35 days.

For the assessment of adverse event rates associated with retreatment, comparisons are made to the first exposure adverse event rates reported for the subset of subjects who were eligible for retreatment. This subset serves as the best available comparison group in the absence of concurrent placebo; however, because this was not a randomized, concurrently treated cohort, comparisons should be interpreted with caution.

During the first 12-week retreatment period, the percentage of subjects with at least one adverse event was approximately 15% lower than that observed during the first exposure period of subjects who were eligible for retreatment. No new pattern of adverse events during retreatment was evident (see Table 37). Acute adverse reactions appeared less common during the second course of Raptiva treatment.

Table 37

Adverse Events Experienced by ≥5% of Subjects Treated with Raptiva following a Period of Non-Treatment

	Raptiva	
Adverse Event	First 12 Weeks [a] (n=1,064)	Retreatment (n=341)
Total [b]	899 (84.5%)	238 (69.8%)
Headache	367 (34.5%)	77 (22.6%)
Infection	155 (14.6%)	57 (16.7%)
Chills	125 (11.7%)	20 (5.9%)
Pain	121 (11.4%)	25 (7.3%)
Pharyngitis	79 (7.4%)	17 (5.0%)
Rhinitis	67 (6.3%)	19 (5.6%)
Psoriasis	42 (3.9%)	18 (5.3%)
Pruritus	42 (3.9%)	17 (5.0%)

[a] Comparisons were made with subjects who completed their first exposure to Raptiva and who were eligible for retreatment.

[b] Represents the number of subjects with at least one adverse event.

Serious adverse events that occurred during a second course of Raptiva treatment are presented in Table 38. Overall, the rates of serious adverse events did not increase with repeat exposure to Raptiva.

Table 38

Serious Adverse Events Reported for 2 or More Subjects during the First or Second Raptiva Treatment Course in the Placebo-Controlled and Open-Label Studies

	Raptiva	
Adverse Event	First 12 Weeks [a] (n = 1,064)	Retreatment (n = 341)
Total [b]	25 (2.3%)	5 (1.5%)
Cellulitus	3 (0.3%)	0
Accidental Injury	2 (0.2%)	0
Arthritis	2 (0.2%)	0
Gastroenteritis	2 (0.2%)	0
Kidney calculus	2 (0.2%)	0

[a] Comparisons were made with subjects who completed their first exposure to Raptiva and who were eligible for retreatment.

[b] Represents the number of subjects with at least one serious adverse event.

6.6 WITHDRAWAL RESULTS

Of the 1,166 subjects observed during 12 weeks of withdrawal or washout from Raptiva, 737 (63.2%) had at least one adverse event. Five types of adverse events (infection, pain, peripheral edema, psoriasis, and pruritus) were reported for ≥ 5% of subjects during washout from treatment with Raptiva. With the exception of psoriasis (13.0%), pruritus (5.6%), and peripheral edema (5.1%), these events occurred at percentages less than, or similar to, those observed for subjects in the first 12-week treatment period of the first exposure cohort (see Section 6.2.4).

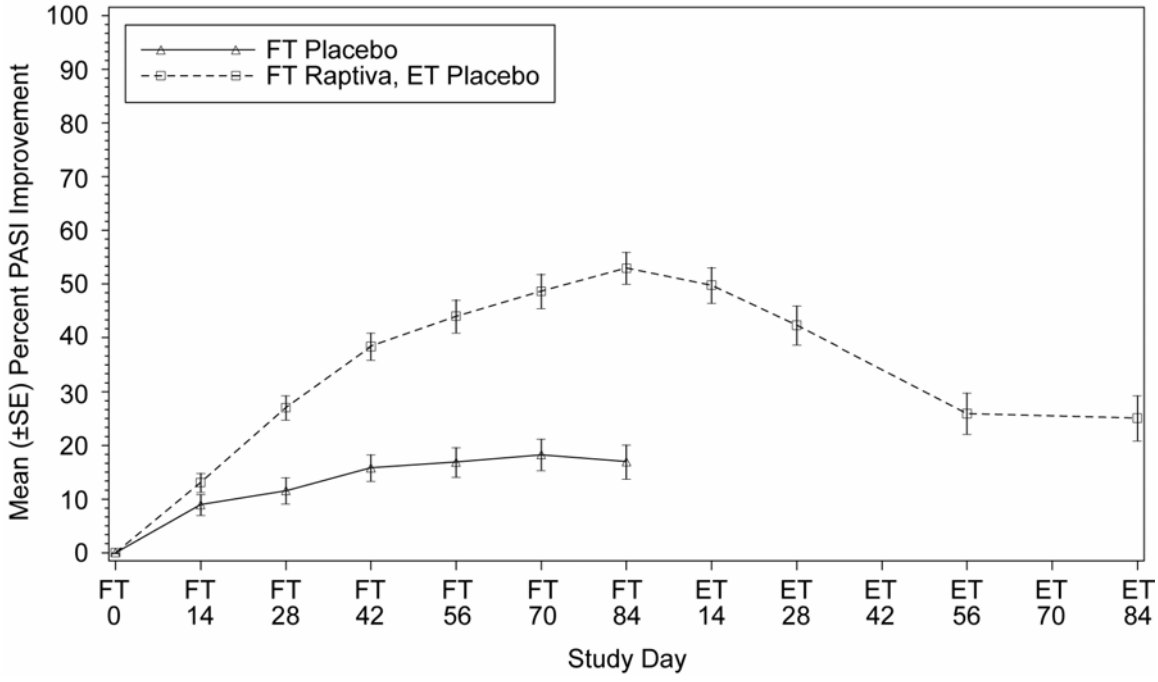
Forty subjects (3.4% of 1,166) reported one or more serious adverse events during the 12 weeks after Raptiva discontinuation. The two most common types of serious adverse events were psoriasis (6 subjects, 0.5%) and

arthritis (3 subjects, 0.3%). The following types of serious adverse events were each reported for 2 subjects (0.2%): accidental injury, anemia, bone disorder (disc herniation), infection, and pneumonia. All other types of serious adverse events occurred in a single subject.

The effects of Raptiva on immune function are reversible, and therefore psoriasis and arthritis return after discontinuation of treatment. Serious and non-serious adverse events of psoriasis were presented in Section 6.2.11. The severity of psoriasis experienced after Raptiva withdrawal was further assessed by examination of PASI scores before, during, and after Raptiva treatment. In general, most subjects experienced a gradual return of PASI score to baseline or somewhat better over a period of weeks (see Figure 13).

Figure 13

Percent PASI Improvement during Raptiva Treatment and Washout for Two Cohorts in Study 2059



In a minority of subjects, the PASI score returned to worse than baseline. The rate of psoriasis overshoot, as defined by the proportion of subjects who had a PASI score at least 25% higher than at baseline at any point during the

12 weeks of follow-up after discontinuation of drug, varied from study to study but was highest in Study 2059, with a rate of 18.2%.

Variability in the natural course of psoriasis as well as in repeat PASI measurements could contribute to the rate of PASI overshoot. An estimate of the extent of variability was obtained using patients who received placebo during the first 12 weeks of the placebo-controlled studies. In Study 2059, 17.8% of placebo subjects experienced a PASI score at least 25% greater than baseline. This suggests that the variability of PASI measurements and the natural history of psoriasis are such that a PASI overshoot rate of 15%–20% is not unexpected over a 12-week period in a group of subjects with moderate to severe plaque psoriasis not receiving therapy for psoriasis.

Consistent with this interpretation, the rate of PASI overshoot in the non-responders (<PASI-50 response) was greater than in the responders (PASI-75 response). In subjects who had less than a PASI-50 response, the rate of PASI overshoot was 29.3%, in subjects who had a PASI-50 (but <PASI-75) response, the rate was 10.6%, and in those who had a PASI-75 response, the rate was 10.0%. Subjects whose PASI scores were near baseline were more likely to have a PASI measurement 25% higher than baseline, probably due to the natural variability of the scores and disease over time.

6.7 DRUG–DRUG AND DRUG–DEMOGRAPHIC INTERACTIONS

6.7.1 Drug–Drug Interactions

Concomitant medications used during the first 12-week treatment period of the Phase III, placebo-controlled studies were reviewed to determine whether they altered the effect of Raptiva on adverse event rates. No pattern suggestive of an interaction between Raptiva and concomitant medications emerged from this review.

Concomitant medications used during the first 12-week treatment period of the Phase III, placebo-controlled studies were reviewed to determine whether they altered the effect of Raptiva on laboratory parameters. There was no indication of any significant interaction between concomitant medications and Raptiva in the effect on laboratory parameters.

6.7.2 Drug–Demographic Interactions

To evaluate the impact of various intrinsic factors on the safety profile of Raptiva, the incidence of adverse events in certain subpopulations of subjects was analyzed for the first 12-week treatment period of Studies 2390, 2600, 2058, and 2059. The following are the intrinsic factors that were analyzed: sex, age, race/ethnicity, baseline PASI category, BMI, and selected conditions in the subject's medical history (allergic reaction, arthritis, autoimmune disease, diabetes mellitus, hyperlipidemia, hypertension, ischemic cardiovascular disease, liver disease, malignancy, and pulmonary disease).

The overall differences between the incidence of adverse events in those with and without the various intrinsic factors were minor and did not appear to indicate any consistent trend other than what would be expected from the underlying condition, and subjects in various intrinsic factor groups did not appear to be at increased risk with Raptiva treatment beyond the inherent risk from their underlying condition.

6.8 DRUG ABUSE, OVERDOSE, AND WITHDRAWAL EFFECTS

No episodes of abuse of Raptiva were identified during the clinical trial program. The potential for drug abuse appears to be very low.

6.9 SELF-ADMINISTRATION OF SUBCUTANEOUS RAPTIVA

Home dosing was permitted following the initial 12-week treatment period in both placebo-controlled and open-label clinical trials. Subjects and caregivers received training and were required to demonstrate ability to self-administer drug. During the second 12 weeks of treatment in Studies 2058 and 2059, between one-third and one-half of the subjects self-administered Raptiva.

The percentages of subjects achieving a PASI-75 at the end of a second 12 weeks of treatment are given in Table 39 for subjects who had not achieved a PASI-75 at the end of the first 12 weeks of treatment with Raptiva. The PASI-75 rates are consistent between those subjects treated in the clinic

and those who received a combination of doses in the clinic and at home during Studies 2058 and 2059.

Table 39

Home Dosing: Subjects without PASI-75 Response during the First 12 Weeks of Treatment Achieving PASI-75 during the Second 12 Weeks of Treatment

Study	Location	Placebo	All Raptiva
2058	Clinic only	7.9% (n=38)	20.3% (n=59)
	Clinic and home	4.5% (n=22)	20.3% (n=64)
2059	Clinic only	3.9% (n=77)	25.5% (n=141)
	Clinic and home	0 (n=28)	24.6% (n=69)

Study 2062 also included subjects or their caregivers who received training and demonstrated ability to self-administer drug during the first three clinic visits to dose at home. A subject assessment of home dosing was conducted at Day 84. Approximately 60% of the subjects in Study 2062 elected to self-administer their Raptiva treatment. Of these subjects, nearly 90% found it easy to self-inject Raptiva and were comfortable with the procedure. More than 70% of these subjects felt Raptiva was more convenient than other psoriasis treatments and were satisfied with their response to Raptiva.

6.10 SAFETY DATA FROM OTHER INDICATIONS

In addition to psoriasis patients, Raptiva has been studied in normal volunteers, asthma patients, transplant patients, rheumatoid arthritis patients, and psoriatic arthritis patients. There were no clinically significant safety signals observed in the normal volunteer and asthma studies. In the transplant study, 2 subjects receiving quadruple immunosuppressive therapy (cyclosporine, prednisone, mycophenolate mofetil, and 2.0 mg/kg/wk Raptiva) and 1 subject who received quintuple immunosuppressive therapy (cyclosporine, prednisone, mycophenolate mofetil, OKT3, and 2.0 mg/kg/wk Raptiva) developed post-transplant lymphoproliferative disorder (PTLD). In 2 subjects, the PTLD resolved, 1 spontaneously and 1 with chemotherapy. The third subject died from sepsis. None of the subjects receiving lower doses of

Raptiva in combination with these other immunosuppressive therapies developed PTLD. A Phase II study evaluating the safety and efficacy of Raptiva in rheumatoid arthritis was recently stopped due to lack of clinical benefit. There were no malignancies or infectious serious adverse events. The psoriatic arthritis study is ongoing. To date, there have been no malignancies or infectious serious adverse events.

6.11 CLINICAL SAFETY SUMMARY AND CONCLUSIONS

Based on data from 2,762 Raptiva-treated subjects with moderate to severe plaque psoriasis, Raptiva appears to be safe and well tolerated. There was no evidence of increased risk for adverse events with increased duration of exposure and no evidence of lymphocyte depletion or clinically significant toxicity affecting bone marrow, liver, kidney, or other organ systems.

The most frequent adverse events were acute adverse reactions (headache, chills, fever, nausea, myalgia), which tended to occur following the initial two injections and were generally mild and self-limited. During the placebo-controlled portions of the Phase III trials, the rates of serious adverse events were low and similar for subjects receiving 1.0 mg/kg/wk SC Raptiva or placebo.

Overall rates of infection and malignancies were low and consistent with the expected background rates. Reversible thrombocytopenia consistent with a drug-induced effect was observed in 6 (0.2%) subjects, but a relationship to Raptiva has not been established. During Raptiva washout, a minority of the subjects experienced an adverse event of psoriasis, possibly due to the restrictions placed on concomitant medications during the washout period.

7. BENEFITS AND RISKS

7.1 UNMET MEDICAL NEED

Psoriasis is frequently disabling and often compromises quality of life. Common physical symptoms that produce impairment include skin pain, itching (often severe), skin tightness, and bleeding. Embarrassment, frustration, fear, and depression are commonly experienced by patients with psoriasis. For many patients, psoriasis is a chronic, life-long disease that impairs quality of life to an extent comparable with arthritis, diabetes, heart disease, or cancer (Koo 1996; Rapp et al. 1999).

Topical medications, such as corticosteroid preparations, calcipotriene (a vitamin D derivative), and tazarotene (a vitamin A derivative) are insufficient to control moderate to severe disease. Currently approved therapies for moderate to severe psoriasis include phototherapy, systemic retinoids, and powerful, relatively non-selective immunosuppressive agents such as cyclosporine and methotrexate (Roenigk et al. 1988; Gottlieb 1998; Lebwohl et al. 1998; Koo 1999; Lebwohl 2000). Although effective, these therapies have significant limitations related to toxicity and accessibility, as listed below.

- Cyclosporine: nephrotoxicity, hypertension, hepatoxicity, vasculopathy, neuropathy, and skin cancer
- Methotrexate: bone marrow failure, liver failure and cirrhosis, severe pulmonary reactions, lymphoma, and severe skin reactions

  Liver biopsies are required after each incremental exposure of 1.5 g.
- Acitretin: long-lasting teratogenicity (3 years after last dose), hyperlipidemia, hepatotoxicity, pancreatitis, hyperostosis, alopecia, and mucosal side effects
- Phototherapy: cutaneous cancers and melanoma

  Access to specialized phototherapy units is limited, and phototherapy requires frequent clinic visits.

There is a clear unmet medical need for the development of safe, convenient, and effective therapies for this serious condition that provide both short- and long-term control.

7.2 BENEFIT–RISK CONCLUSIONS

Subjects receiving Raptiva therapy experience rapid and sustained improvement in their signs and symptoms of psoriasis. Close to one-third of the subjects experienced a ≥75% reduction in their PASI score 12 weeks after initiation of therapy, while well over 40% experienced this benefit by 24 weeks after treatment. The number of subjects who had ≥50% reduction in PASI score at these timepoints was even higher: nearly two-thirds of subjects achieved a PASI-50 response by 24 weeks of therapy. Other symptoms, including itching and quality-of-life, also significantly improved and maintained while subjects were on therapy.

Raptiva has been studied in a large number of subjects and was shown to be well tolerated. There were few serious adverse events observed in subjects receiving Raptiva therapy, and no evidence of increased incidence of malignancy, lymphocyte suppression, bone marrow suppression, or other serious organ toxicity with long-term therapy. Discontinuations, particularly discontinuations due to adverse events, were infrequent. Most of the non-serious adverse events were transient and resolved after initiation of appropriate therapy.

Therapy with Raptiva has been demonstrated to offer convenient, continuous control of psoriasis with an acceptable safety and tolerability profile. The benefits experienced by most subjects treated with Raptiva outweigh any potential, infrequent risks. In addition, the absence of specific cumulative organ toxicity appears to obviate the need for rotational therapy with this agent. Raptiva provides a significant new, safe, and efficacious alternative for patients with moderate to severe plaque psoriasis.

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APPENDIX A
Proposed Package Insert

RAPTIVA™
[Efalizumab]

DESCRIPTION

RAPTIVA™ (Efalizumab) is a recombinant humanized IgG1 kappa isotype monoclonal antibody that selectively binds to human CD11a. CD11a is the α subunit of leukocyte function antigen-1 (LFA-1), a β2 integrin, and is expressed on all leukocytes. Efalizumab contains human framework regions with the complementarity-determining regions of a humanized murine antibody that binds to CD11a (1). Efalizumab is produced by recombinant DNA technology in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and is purified by a process that includes specific viral inactivation and removal steps. Gentamicin is not detectable in the final product. Efalizumab consists of 1328 amino acids and has a molecular weight of approximately 150 kilodaltons.

RAPTIVA is supplied as a sterile, white to off-white, lyophilized powder in single-use glass vials for subcutaneous (SC) injection. After reconstitution with 1.3 mL of supplied Sterile Water for Injection for Reconstitution, the solution of RAPTIVA is clear to pale yellow with a pH of approximately 6.2. Each vial contains approximately 1.5 mL of solution to deliver 1.25 mL (125 mg) of drug product. Each 1.25 mL RAPTIVA contains 125 mg efalizumab, 9.25 mg histidine, 102.7 mg sucrose, and 2.5 mg polysorbate 20.

CLINICAL PHARMACOLOGY

General

The interaction between LFA-1 and intercellular adhesion molecule-1 (ICAM-1) plays a major role in the dermal and epidermal accumulation of lymphocytes in psoriasis. Overall the engagement of LFA-1 and ICAM-1 results in the initiation and maintenance of multiple functions, including activation of T lymphocytes, adhesion of T lymphocytes to endothelial cells, and migration of T lymphocytes to sites of inflammation. In psoriatic skin, ICAM-1 is upregulated on endothelium and

keratinocytes. Efalizumab binds specifically to CD11a (the α subunit of LFA-1) on T lymphocytes, inhibits the binding of LFA-1 to ICAM-1, and results in inhibition of T lymphocyte adhesion to other cell types. This results in reduced inflammation by any or all of the following mechanisms: inhibition of CD11a expression; inhibition of T lymphocyte proliferation, interleukin-2 receptor expression and cytokine release; inhibition of T lymphocyte trafficking to psoriatic lesions; inhibition of T lymphocyte interaction with keratinocytes.

CD11a is also expressed on the surface of B lymphocytes, monocytes, neutrophils, natural killer cells and other leukocytes. Therefore, the potential exists for RAPTIVA to affect the activation, adhesion and numbers of cells other than T lymphocytes.

Pharmacokinetics

In patients with moderate to severe plaque psoriasis, using an initial SC RAPTIVA dose of 0.7 mg/kg followed by 11 weekly SC doses of 1 mg/kg/wk, serum concentrations reached a steady-state by 4 weeks with mean trough and peak concentrations of approximately 9 μg/mL and 12 μg/mL, respectively. Steady-state clearance was 24 mL/kg/day (range $=5-76$ mL/kg/day, n $=25$). Average time taken to eliminate RAPTIVA after the last steady-state dose was 25 days (range $=13-35$ days, n $=17$). Average RAPTIVA SC bioavailability was estimated to be 50%. Weight was found to be the most significant covariate affecting RAPTIVA clearance. RAPTIVA clearance was not significantly affected by gender, race, age, baseline PASI, or baseline lymphocyte count.

The pharmacokinetics of RAPTIVA in pediatric patients have not been studied. The effects of renal or hepatic impairment on the pharmacokinetics of RAPTIVA have not been studied.

Pharmacodynamics

At a dose of 1 mg/kg/wk SC, RAPTIVA reduced expression of CD11a on circulating T lymphocytes to approximately 15–25% of pre-dose values and saturated CD11a to <5% of baseline available CD11a binding sites. Full effect was seen within 1–2 days after the first dose, and was maintained between weekly doses. CD11a levels returned to within 25% of baseline within 5–8 weeks following the discontinuation of RAPTIVA.

In clinical trials, RAPTIVA therapy resulted in a doubling of mean lymphocyte counts relative to baseline presumably due to the reversal of leukocyte adhesion to the blood vessel walls. The mean absolute lymphocyte count was within the normal range during treatment; however lymphocyte counts did increase above normal limits for some patients. Lymphocyte counts did not increase further with continued treatment and returned to baseline values approximately 6 weeks after drug discontinuation.

CLINICAL STUDIES

RAPTIVA was evaluated in three randomized, double-blind, placebo-controlled studies in adults with chronic (> 6 months) plaque psoriasis and a minimum body surface area involvement of 10%. Doses of 1 mg/kg or 2 mg/kg or placebo were administered once a week for 12 consecutive weeks. Results from patients receiving 1 mg/kg/wk are presented as that is the recommended dose. Patients could receive concomitant low potency topical steroids. No other concomitant psoriasis therapies were allowed during treatment or the follow-up period.

Table 1 shows the primary endpoint results for the first 12-week treatment course of Studies 1, 2 and 3. The primary endpoint was defined as the proportion of patients with a reduction in score on the Psoriasis Area and Severity Index (PASI) of at least 75% from baseline at one week following the 12-week treatment period.

Table 1

Primary Endpoint: Proportion of Patients with ≥75% Improvement in PASI After 12 Weeks of Treatment (PASI-75)

	Placebo	RAPTIVA 1 mg/kg/wk	Difference (95%CI)
Study 1	4% n=187	27%[a] n=369	22% (16%, 29%)
Study 2 [b, c]	2% n=170	39%[a] n=162	37% (28%, 46%)
Study 3 [b, c]	5% n=122	22%[a] n=232	18% (9%, 27%)

[a] $p < 0.001$ for comparison of Raptiva-treated group with placebo-treated group using Fisher's exact test within each study.

[b] Studies performed with a closely related efalizumab by a different manufacturer.

[c] Studies also evaluated 2 mg/kg/wk RAPTIVA. Response rates of patients receiving 2 mg/kg/wk were similar to those presented for 1 mg/kg/wk.

Other efficacy endpoints listed in Table 2 included the proportion of patients who achieved a score of "minimal" or "clear" by the Overall Lesion Severity (OLS); "excellent" or "clear" by the Physician's Global Assessment of Change (PGA); the proportion of patients with a reduction in PASI of at least 50% from baseline one week following the 12 week treatment period.

Table 2

Secondary Endpoints: After 12 Weeks of Treatment

	Study	Placebo	RAPTIVA 1 mg/kg/wk
OLS: Minimal or Clear	Study 1	3%	26%[a]
	Study 2	3%	32%[a]
	Study 3	3%	19%[a]
PGA: Excellent or Cleared	Study 1	5%	33%[a]
	Study 2	4%	39%[a]
	Study 3	4%	22%[a]
Proportion of Patients with ≥50% improvement in PASI after 12 weeks of treatment (PASI-50)	Study 1	14%	59%[a]
	Study 2[b]	15%	61%[a]
	Study 3[b]	16%	52%[a]

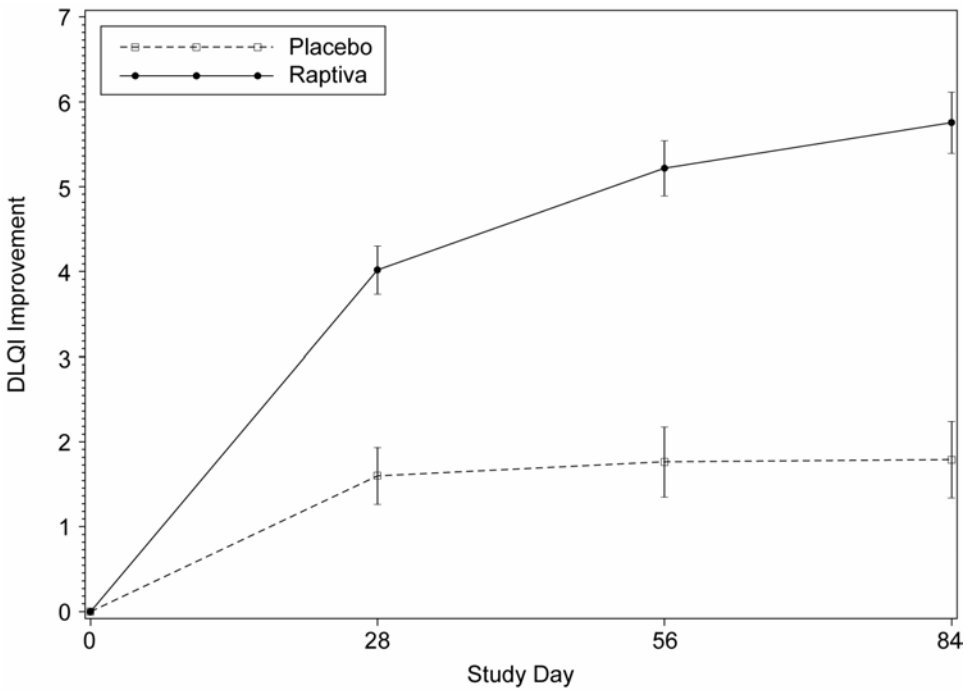
[a] $p < 0.001$ for comparison of Raptiva-treated group to placebo-treated group using Fisher's exact test.

[b] PASI-50 was not a prespecified endpoint in this study.

Mean psoriasis body surface area involvement at baseline was approximately 30%. With RAPTIVA treatment, the percentage of body surface area affected by psoriasis decreased to approximately 18% among RAPTIVA treated patients compared with approximately 28% among placebo treated patients.

Between baseline and week 12, RAPTIVA treated patients experienced significantly greater improvement than placebo in health outcomes as assessed by the Dermatology Life Quality Index (DLQI, Figure 1) (2), the Psoriasis Symptom Assessment Frequency and Severity sub-scales, and Itch-specific scales (all $p < 0.001$). The improvement in DLQI for RAPTIVA treated patients compared with placebo treated patients was observed for all domains (Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, Treatment). For Study 1, 70% of the DLQI improvement was observed by week 4 of treatment.

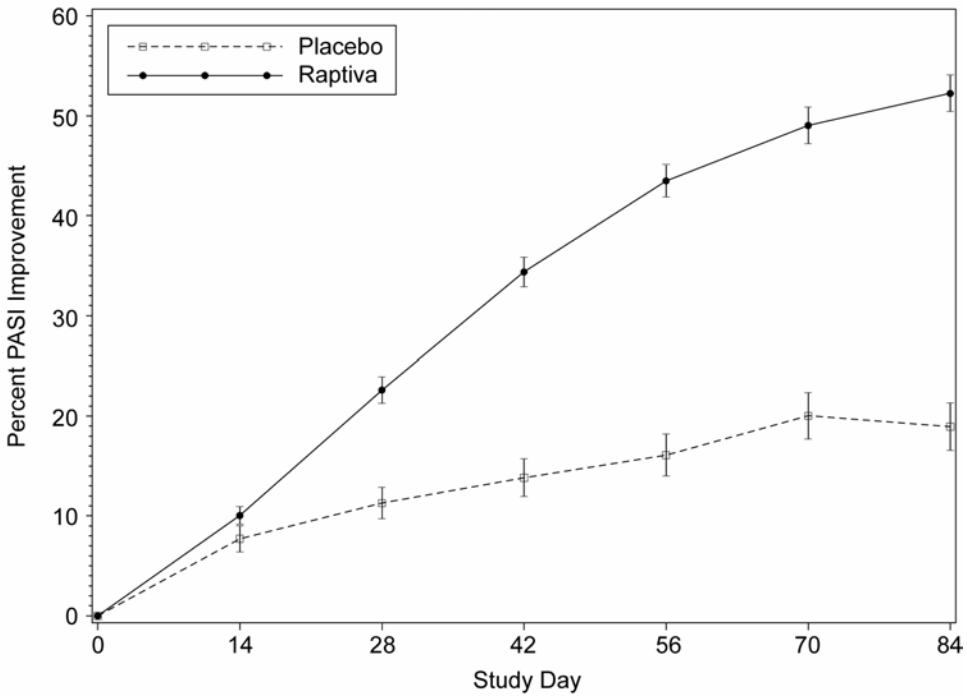
Figure 1
Mean Improvement in DLQI Versus Study Day during
First 12 Weeks of Treatment in Study 1 (Mean ± SEM)[a]



[a] The mean improvement in DLQI overall score, baseline to Day 84, was 5.6 for RAPTIVA and 1.6 for placebo ($p < 0.001$; Wilcoxon rank-sum test of difference in DLQI change score, RAPTIVA vs. placebo).

There was a significantly greater improvement in the PASI score in the RAPTIVA treated patients compared with placebo treated patients after 2 weeks of treatment, and there was continuous improvement over the 12-week treatment period for the RAPTIVA treated patients (Figure 2). In controlled trials of continuous RAPTIVA treatment greater than 12 weeks, the percent of patients who have more than a 75% reduction in PASI continues to increase.

Figure 2
Percent PASI Improvement Versus Study Day during
First 12 Weeks of Treatment in Study 1 (Mean ± SEM)



After 12 weeks of treatment with 1 mg/kg, the median duration of response (defined as maintenance of a 75% or greater reduction in PASI) was approximately 55 days for RAPTIVA treated patients.

In an open-label study of 290 patients treated with RAPTIVA who achieved 50% or greater reduction in PASI or an OLS rating of Clear, Minimal or Mild after the first 12-weeks of RAPTIVA treatment and were continuously treated for one year (48 weeks), approximately 57% of patients achieved a 75% or greater reduction in PASI. A controlled retreatment study (Study 2) demonstrated that after a treatment interruption, patients could restart RAPTIVA treatment and achieve improvements in PASI. In Study 3, patients who reached a 75% or greater reduction in PASI after 12 weeks of RAPTIVA treatment with 1 mg/kg/wk or 2 mg/kg/wk maintained a 50% or

greater reduction in PASI with an additional 12 weeks of treatment at a dose of 2 mg/kg every other week.

INDICATIONS AND USAGE

RAPTIVA is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis.

CONTRAINDICATIONS

RAPTIVA should not be administered to patients with known hypersensitivity to RAPTIVA or any of its components.

WARNINGS

None.

PRECAUTIONS

General

Abrupt discontinuation of RAPTIVA may be followed by worsening of psoriasis or emergence of new psoriasis morphologies, including erythrodermic and pustular psoriasis.

Immunosuppression

RAPTIVA has not been studied extensively in combination with immunosuppressive agents in psoriasis patients and should be used cautiously in this setting.

The possibility exists for any therapy that affects immune function, including RAPTIVA, to affect host defenses against infections and malignancies.

The role of RAPTIVA in the development and course of malignancies as well as active and/or chronic infections is not fully understood (see ADVERSE REACTIONS). The safety and efficacy of RAPTIVA in psoriasis patients with pre-existing immunosuppression or chronic infections have not been evaluated.

Immunizations

The safety and efficacy of vaccines specifically live or live-attenuated vaccines, administered to patients being treated with RAPTIVA have not been studied.

Information for Patients

If a patient or caregiver is to administer RAPTIVA, he/she should be instructed regarding injection techniques and how to measure the correct dose to ensure proper administration of RAPTIVA. A puncture-resistant container for disposal of needles and syringes should be used. Patients and caregivers should be instructed regarding technique as well as proper syringe and needle disposal and be cautioned against reuse of these items (see Information for Patients and Caregivers).

Patients should be advised to inform their physician promptly if they develop any signs of an infection or malignancy while undergoing treatment with RAPTIVA.

Female patients should also be advised to notify their physicians if they become pregnant while taking RAPTIVA.

Drug Interactions

There have been no formal drug interaction studies performed with RAPTIVA. Caution should be employed when RAPTIVA is used with immunosuppressive drugs (see PRECAUTIONS, Immunosuppression).

RAPTIVA has been used in combination with topical tar or corticosteroids (Classes I to VII) and ultraviolet B in psoriasis patients. Concomitant use of these treatments did not appear to affect safety.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of RAPTIVA. No lymphomas were observed when mice susceptible to

develop lymphoma were treated for 6 months with an anti-mouse CD11a antibody; one lymphoma was observed in placebo treated mice. This strain of mice was previously shown to develop lymphomas during 6 months of cyclosporine treatment (3).

In a fertility and general reproduction study with an anti-mouse CD11a antibody, no adverse effects were noted on mating, fertility, or reproduction parameters in male and female mice.

Mutagenicity studies were not conducted.

Pregnancy Category B

Women of childbearing potential make up a considerable segment of the patient population affected by psoriasis. Since the effect of RAPTIVA on pregnancy and fetal development (including immune system development) is not known, RAPTIVA should be used during pregnancy only if clearly needed.

Reproduction studies have not been conducted with RAPTIVA. It is not known whether RAPTIVA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. In general, immunoglobulins are known to cross the placental barrier; therefore, RAPTIVA should be given to a pregnant woman only if clearly needed.

In a developmental toxicity study conducted in mice using an anti-mouse CD11a antibody, no evidence of maternal toxicity, embryotoxicity, or teratogenicity was observed. No adverse effects on behavioral, reproductive or growth parameters were observed in offspring of female mice exposed to an anti-mouse CD11a antibody during gestation and lactation. At 11 weeks of age, the offspring had intact cell-mediated immunity and a reduction in the primary antibody response. At 25 weeks of age, the offspring had a normal primary antibody response. Animal

studies, however, are not always predictive of human response and there are no adequate and well-controlled studies in pregnant women. Because the risk to the development of the fetal immune system and postnatal immune function in humans is unknown, RAPTIVA should be used during pregnancy only if clearly needed. If pregnancy occurs while taking RAPTIVA, continued use of the drug should be assessed.

Nursing Mothers

It is not known whether RAPTIVA is excreted in human milk. An anti-mouse CD11a antibody was detected in milk samples of exposed lactating mice. Because many drugs are excreted in human milk, and because there exists the potential for serious adverse reactions in nursing infants from RAPTIVA, a decision should be made whether to discontinue nursing while taking the drug or to discontinue the use of the drug, taking into account the importance of the drug to the mother.

Geriatric Use

Of the 1620 patients who received RAPTIVA in controlled trials, 128 were $\geq$65 years of age, and 2 were $\geq$75 years of age. No differences in safety or efficacy were observed between older and younger patients, but there were not sufficient data to exclude important differences. Because the incidence of infections is higher in the elderly population, in general, caution should be used in treating the elderly.

Pediatric Use

The safety and efficacy of RAPTIVA in pediatric patients have not been studied. RAPTIVA is not indicated for pediatric patients.

ADVERSE REACTIONS

The most serious adverse reaction was:

- Serious infections requiring hospitalization (see ADVERSE REACTIONS, Infections)

The most common adverse events associated with RAPTIVA exposure were a symptom complex of mild to moderate headache, chills, fever, nausea or myalgia within two days following the first two injections (Table 3). In placebo-controlled trials, 29% of patients treated with RAPTIVA 1 mg/kg developed these symptoms following the first dose compared with 15% of patients receiving placebo. Following the third and subsequent weekly injections, only 4% and 3% of patients receiving RAPTIVA 1 mg/kg and placebo, respectively, experienced these symptoms. Less than 1% of patients discontinued RAPTIVA treatment because of these generally mild to moderate adverse events.

Table 3

Adverse Events in Phase III Studies Reported at a Rate of at Least 5% in the 1 mg/kg/wk, 2 mg/kg/wk RAPTIVA Treatment or Placebo-treated groups

	Placebo (n=715)	RAPTIVA 1 mg/kg/wk (n=1213)	RAPTIVA 2 mg/kg/wk (n=407)
Headache [a]	159 (22%)	391 (32%)	151 (37%)
Infection [b]	188 (26%)	350 (29%)	114 (28%)
Chills [a]	32 (4%)	154 (13%)	53 (13%)
Nausea [a]	51 (7%)	128 (11%)	56 (14%)
Pain	38 (5%)	122 (10%)	45 (11%)
Myalgia [a]	35 (5%)	102 (8%)	32 (8%)
Pharyngitis	47 (7%)	88 (7%)	31 (8%)
Flu Syndrome	29 (4%)	83 (7%)	19 (5%)
Asthenia	37 (5%)	81 (7%)	38 (9%)
Rhinitis	46 (6%)	81 (7%)	17 (4%)
Fever [a]	24 (3%)	80 (7%)	46 (11%)
Diarrhea	48 (7%)	72 (6%)	30 (7%)
Accidental Injury	45 (6%)	68 (6%)	27 (7%)
Sinusitis	34 (5%)	63 (5%)	14 (3%)
Back Pain	14 (2%)	50 (4%)	25 (6%)

[a] These events were mostly mild to moderate and usually occurred within 48 hours of first two RAPTIVA injections.

[b] Includes diagnosed infections and other non-specific infections. Most common non-specific infection was upper respiratory infection.

The proportion of patients who discontinued treatment due to non-serious adverse events during the placebo-controlled portion of the Phase III studies was 2.8% for patients taking RAPTIVA and 1.8% for placebo treated patients. The most common non-serious adverse events resulting in discontinuation of RAPTIVA treatment were headache (0.6%), psoriasis (0.6%), pain (0.4%), arthritis (0.4%) and arthralgia (0.3%).

Adverse events experienced during a second RAPTIVA treatment course were similar to those observed during a first 12-week course, with the exception of fewer acute adverse reactions.

No new common adverse events emerged when RAPTIVA treatment was extended up to 60 weeks.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The data described below reflect exposure to RAPTIVA in a total of 2762 psoriasis patients in 13 studies of RAPTIVA. Approximately 2400 patients received RAPTIVA weekly for 12 weeks of continuous treatment, 904 for 24 weeks of continuous treatment, and 218 for 1 year of continuous treatment. Approximately 340 received two separate 12-week courses of RAPTIVA. Approximately 2335 psoriasis patients were studied in Phase III, placebo-controlled, double-blind, randomized trials. The population ranged in age from 18 to 75 years and included 67% men and 33% women. The patients were mostly Caucasian (89%), reflecting the general psoriatic population. Disease severity at baseline was moderate to severe psoriasis.

Malignancies

The overall incidence of malignancies was 1.7 per 100 patient-years for RAPTIVA treated patients compared with 1.6 per 100 patient-years for placebo treated patients.

Among the 2762 psoriasis patients who received RAPTIVA at any dose, 30 patients were diagnosed with 36 malignancies during RAPTIVA treatment. The majority of

these malignancies (26 cases in 20 patients, 0.7% of 2762 patients) were basal (13 cases) and squamous (13 cases) cell cancers of the skin. The incidence of basal and squamous cell skin cancers was comparable for RAPTIVA-treated patients and those receiving placebo. Eight solid tumor malignancies were observed. One lymphoma diagnosed as Hodgkin's lymphoma and one malignant melanoma were also observed. The incidence of non-cutaneous solid tumors, lymphoproliferative disorders, and malignant melanoma were within the range expected for the general population.

Infections

The overall incidence of hospitalized infections was 1.6 per 100 patient-years for RAPTIVA treated patients compared with 1.1 per 100 patient-years for placebo treated patients. Twenty-seven of 2475 RAPTIVA treated patients had infections leading to hospital admission. These infections included cellulitis, pneumonia, abscess, sepsis, bronchitis, gastroenteritis, aseptic meningitis, Legionnaire's disease, and vertebral osteomyelitis. The observed number of infections resulting in hospitalization was within the expected range for this patient population. There were no deaths due to infection. Less than 1% of patients treated with RAPTIVA discontinued treatment because of an infection.

Hypersensitivity Reactions

No episodes of anaphylaxis occurred in clinical trials of RAPTIVA. Urticaria was observed in less than 1% of patients receiving placebo and approximately 1% of patients receiving RAPTIVA during the initial 12-week treatment period. For those patients who were rechallenged it was without incident, so relationship to treatment is not evident. Other adverse events possibly indicative of hypersensitivity included: bronchiolitis obliterans, laryngospasm, angioedema, erythema multiforme, asthma, allergic drug eruption and possible serum sickness.

Immunogenicity

Patients were tested for antibodies to RAPTIVA at multiple timepoints during and after treatment. After RAPTIVA treatment ended, predominantly low-titer antibodies to RAPTIVA or other protein components of the RAPTIVA drug product were detected in 6.3% (67/1063) of RAPTIVA treated patients. There were no significant differences in pharmacokinetics, pharmacodynamics, clinically important adverse events or clinical response between antibody-positive and antibody-negative patients. The long-term immunogenicity of RAPTIVA is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to RAPTIVA in the ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RAPTIVA with the incidence of antibodies to other products may be misleading.

Other Observed Adverse Reactions from Clinical Trials

Less common events that were observed at a higher rate in RAPTIVA treated patients include thrombocytopenia, arthritis, and new forms of psoriasis including erythrodermic and pustular psoriasis.

OVERDOSAGE

Doses up to 4 mg/kg/wk SC for 10 weeks have been administered without any toxic effect. The maximum administered single dose was 10 mg/kg IV. This was administered to one patient, who subsequently was admitted to the hospital for severe vomiting. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

APPENDIX A (cont'd)
Proposed Package Insert

DOSAGE AND ADMINISTRATION

Usual Dose

The recommended dose of RAPTIVA is a single 0.7 mg/kg SC conditioning dose followed by weekly SC doses of 1 mg/kg (maximum single dose not to exceed a total of 200 mg).

RAPTIVA is intended for use under the guidance and supervision of a physician. Patients may self-inject RAPTIVA if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training of injection technique.

Preparation for Administration

RAPTIVA should be administered using the sterile, disposable syringe and needles provided (see How Supplied section). Remove the cap from the pre-filled syringe containing Sterile Water for Injection for Reconstitution. Attach needle to syringe. Before needle insertion, remove the plastic cap protecting the rubber stopper of the RAPTIVA vial. Do not touch the top of the vial. To prepare the RAPTIVA solution, slowly inject the 1.3 mL of Sterile Water for Injection for Reconstitution in the provided pre-filled syringe into the RAPTIVA vial. Swirl the product vial with a GENTLE rotary motion. DO NOT SHAKE. Shaking will cause foaming of the RAPTIVA solution. Generally, dissolution of RAPTIVA takes less than 5 minutes. The reconstituted solution should be clear to pale yellow. Because RAPTIVA contains no antibacterial preservatives it should be reconstituted immediately before use and used once only. If the reconstituted RAPTIVA is not used immediately, store the RAPTIVA vial at room temperature and use within 8 hours.

Administration

The solution in the vial should be carefully inspected visually for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, the product should not be used.

Replace the needle on the syringe with a new needle. Insert the needle into the vial containing the RAPTIVA solution, invert the vial and, taking care to keep the needle below the level of the liquid, withdraw the solution into the syringe, removing from the vial only the dose to be given.

No other medications should be added to solutions containing RAPTIVA, and RAPTIVA should not be reconstituted with other diluents.

Sites for injection include thigh, abdomen, buttocks or upper arm. Injection sites should be rotated.

Following administration, discard any unused reconstituted RAPTIVA solution.

Stability and Storage

Do not use a vial beyond the expiration date stamped on the carton or vial label. RAPTIVA (lyophilized powder) must be refrigerated at 2–8°C (36–46°F). Protect the vial from exposure to light. Store in original carton until time of use.

HOW SUPPLIED

RAPTIVA is supplied as a lyophilized, sterile powder, designed to deliver 125 mg of efalizumab per vial.

Each RAPTIVA carton contains four trays. Each tray contains one 125 mg vial of RAPTIVA, one 1.3 mL pre-filled syringe containing Sterile Water for Injection for Reconstitution, two alcohol prep pads, and two 25 × 5/8" needles. Carton NDC 50242-058-04.

REFERENCES

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RAPTIVA™ [Efalizumab]

Manufactured by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA
94080-4990

4826400 (974)
FDA Approval Date (Month)
(Year)

APPENDIX B
Psoriasis Area and Severity Index

Evaluator Requirements

- The evaluator must be a dermatologist or experienced physician.
- The evaluator must have attended the Investigator Meeting or have been trained by someone who attended the Investigator Meeting.
- The same evaluator must determine all PASIs for any individual subject throughout the trial.

  A backup evaluator is only allowed in case of emergency or special situation when the designated evaluator is unable to perform the evaluation. The backup evaluator must be a dermatologist or an experienced physician and have attended the Investigator meeting or have been trained by someone who attended the Investigator meeting.

General Instructions

1. For each area of the body, rate erythema, scaling, and thickness for the **average** plaque or the overall condition of plaques in that region.
2. Rate plaques as they are actually seen on the day of examination. Do not rate in comparison with baseline condition.

PASI Scoring

PASI scores can range from 0 to 72. Dermatologic disease severity is to be scored as follows:

Body Areas

Four main body areas will be assessed, the head (h), the trunk (t), the upper extremities (u), and the lower extremities (l) corresponding to 10%, 30%, 20%, and 40% of the total body surface area (BSA), respectively.

APPENDIX B (cont'd)
Psoriasis Area and Severity Index

The area of psoriatic involvement for each body area (Ah, At, Au, Al) will be assigned a numerical value according to degree of involvement as follows:

0 = no involvement
1 = <10% involvement
2 = 10% to <30% involvement
3 = 30% to <50% involvement
4 = 50% to <70% involvement
5 = 70% to <90% involvement
6 = 90% to 100% involvement

Conventions for estimating BSA include the following:

Include only currently active disease in affected area:

For small, scattered lesions do not include the skin between the lesions in the estimate;

For a centrally cleared plaque, count only area of inflamed outer ring;

Do not include residual hyperpigmentation, hypopigmentation, pigmented macules, or diffuse slight pink coloration

- Assignments for the following body segments are:

Neck: include with the head
Buttocks: include with the lower extremities
Axillae: include with trunk
Genitals: include with the trunk
Separation of trunk and lower extremities: the inguinal canal separates the trunk and legs anteriorly

<u>Psoriatic Lesion Signs</u>

In addition, the severity of the psoriatic lesions in three main signs—erythema (E), thickness (T), and scaling (S)—will be assessed for each body area according to a scale (0–4) in which 0 represents a complete lack of cutaneous involvement and 4 represents the most severe possible involvement.

APPENDIX B (cont'd)
Psoriasis Area and Severity Index

	Erythema [a]	Scaling	Thickness
0=none	No redness	No scaling	No elevation over normal skin
1=slight	Faint redness	Fine scale partially covering lesions	Slight but definite elevation, typically edges indistinct or sloped
2=moderate	Red coloration	Fine to coarse scale covering most of all of the lesions	Moderate elevation with rough or sloped edges
3=severe	Very or bright red coloration	Coarse, non-tenacious scale predominates covering most or all of the lesions	Marked elevation typically with hard or sharp edges
4=very severe	Extreme red coloration; dusky to deep red coloration	Coarse, thick, tenacious scale over most or all lesions; rough surface	Very marked elevation typically with hard sharp edges

[a] Do not include residual hyperpigmentation, hypopigmentation, pigmented macules, or diffuse slight pink coloration as erythema.

APPENDIX B (cont'd)
Psoriasis Area and Severity Index

Calculating PASI

To calculate the PASI, the sum of the severity rating for the three main signs will be multiplied with the numerical value of the area affected and with the various percentages of the four body areas. These values will then be added to complete the formula as follows:

$$\text{PASI} = 0.1\,(Eh + Th + Sh)\,Ah + 0.3\,(Et + Tt + St)\,At + 0.2\,(Eu + Tu + Su)\,Au + 0.4\,(El + Tl + Sl)\,Al$$

Row		Head	Trunk	Upper Limbs	Lower Limbs
1	Erythema [a]				
2	Thickness [a]				
3	Scaling [a]				
4	Total each column				
5	Degree of involvement [b]				
6	Multiply Row 4 by Row 5				
7		× 0.10	× 0.30	× 0.20	× 0.40
8	Multiply Row 6 by Row 7				
9	Total PASI (add together each column from Row 8)				

[a] Rank severity of psoriatic lesions: 0=none, 1=slight, 2=moderate, 3=severe, 4=very severe.

[b] Rank area of psoriatic involvement: 0=none, 1= <10%, 2=10% to <30%, 3=30% to <50%, 4=50% to <70%, 5=70% to <90%, 6=90% to 100%.

APPENDIX C
Physicians Global Assessment
(Formerly known as the Overall Lesion Severity Scale)

The degree of overall lesion severity will be evaluated using the following categories:

Score	Category	Category Description
0	Clear	Plaque elevation = 0 (no elevation over normal skin) Scaling = 0 (no scale) Erythema = ± (hyperpigmentation, pigmented macules, diffuse faint pink or red coloration)
1	Minimal	Plaque elevation = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) Scaling = ± (surface dryness with some white coloration) Erythema = up to moderate (up to definite red coloration)
2	Mild	Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped) Scaling = fine (fine scale partially or mostly covering lesions) Erythema = up to moderate (up to definite red coloration)
3	Moderate	Plaque elevation = moderate (moderate elevation with rough or sloped edges) Scaling = coarser (coarse scale covering most of all of the lesions) Erythema = moderate (definite red coloration)
4	Severe	Plaque elevation = marked (marked elevation typically with hard or sharp edges) Scaling = coarse (coarse, non-tenacious scale predominates covering most or all of the lesions) Erythema = severe (very bright red coloration)
5	Very severe	Plaque elevation = very marked (very marked elevation typically with hard sharp edges) Scaling = very coarse (coarse, thick tenacious scale over most of all of the lesions; rough surface) Erythema = very severe (extreme red coloration; dusky to deep red coloration)

Note: Presented by Hon-Sum Ko, M.D., Medical Officer, Division of Dermatologic and Dental Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration. Bethesda (MD): Dermatologic and Ophthalmic Advisory Committee 49th Meeting; 20 March 1998.

APPENDIX C (cont'd)
Physicians Global Assessment
(Formerly known as the Overall Lesion Severity Scale)

The PGA score should be selected using the descriptors that best describe the overall appearance of the lesions. It is not necessary that all three criteria be fulfilled. In some subjects either scale or erythema will dominate the clinical presentation. In those cases, the PGA score should be based on a combination of plaque elevation and the dominant feature (either erythema or scale). Because plaque elevation is the most robust finding, it should be the dominant feature influencing the PGA rating for indeterminant cases.

Evaluator Requirements

The evaluator must be a dermatologist or an experienced physician.

The evaluator must have attended the Investigator meeting or have been trained by someone who attended the Investigator meeting.

The same evaluator should determine all PGA ratings for any individual subject throughout the trial.

A backup evaluator is only allowed in case of emergency or special situation when the designated evaluator is unable to perform the evaluation. The backup evaluator must be a dermatologist or experienced physician and have attended the Investigator meeting or have been trained by someone who attended the Investigator meeting.

APPENDIX D
Physician's Global Assessment of Change

The global response of all psoriatic lesions to therapy compared with the baseline condition using Day 0 photographs will be evaluated using the following categories:

Category	Percent Improvement	Category Description
Cleared	100%	Remission of all clinical signs and symptoms compared with baseline, except for residual manifestations such as mild erythema
Excellent	75%–99%	Improvement of all clinical signs and symptoms compared with baseline, except for residual manifestations such as mild erythema
Good	50%–74%	Improvement of all clinical signs and symptoms compared with baseline
Fair	25%–49%	Improvement of all clinical signs and symptoms compared with baseline
Slight	1%–24%	Improvement of all clinical signs and symptoms compared with baseline
Unchanged		Clinical signs and symptoms unchanged from baseline
Worse		Clinical signs and symptoms deteriorated from baseline

Instructions

- All ratings must be determined using the FT Day 0 medical photographs for comparison.
- The evaluator must be a dermatologist or experienced physician.
- The evaluator must have attended the Investigator Meeting or been trained by someone who attended the Investigator Meeting.
- The same evaluator must perform all determinations of PGAs for any individual subject throughout the study.
- The PGA score should, at minimum, include and reflect a global consideration of erythema, scaling, plaque thickness, and percentage of total body surface area affected by psoriasis.

APPENDIX D (cont'd)
Physician's Global Assessment of Change

Instructions (cont'd)

- The same evaluator should perform all determinations of PGA for any individual subject throughout the study.

  A backup evaluator is only allowed in case of emergency or special situation when the designated evaluator is unable to perform the evaluation. The backup evaluator must be a dermatologist or experienced physician and have attended the Investigator meeting or have been trained by someone who attended the Investigator meeting.

- The PGA score should, at a minimum, include and reflect a global consideration of erythema, scaling, plaque thickness, and percentage of total body surface area affected by psoriasis.
- At each visit, the PGA should be performed after the determination of the Psoriasis Area and Severity Index, Overall Lesion Severity, Psoriasis body surface area, Itching Scale, and Psoriasis Symptom Assessment.
- Do not include residual marks from lesions (e.g., mild erythema, pigmented macules, hyperpigmentation, hypopigmentation) in determination of the PGA.
- The evaluator may reference the CRFs, scales, source document notes, or any other relevant information from prior visits to assist him or her in determining the PGA.

Note: Percentages relate to **improvement for that subject**. They are not a rating of how the subject's improvement corresponds to improvement seen in other patients who are using other medications.

APPENDIX E
Copies of Publications

Copies of all manuscript articles listed in the reference list are included in this appendix.