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A Phase I Study Evaluating the Safety, Pharmacokinetics, and Clinical Response of a Human IL-12 p40 Antibody in Subjects with Plaque Psoriasis

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The potential therapeutic activity of a human monoclonal antibody to the human interleukin-12 p40 subunit (anti-IL-12p40) has been established both *in vitro* and *in vivo*, warranting a first-in-human investigation in psoriasis. This phase I, first-in-human, non-randomized, open-label study evaluated the short-term safety, pharmacokinetics, and clinical response of single, ascending, intravenous (IV) doses of anti-IL-12p40 in subjects with moderate-to-severe psoriasis vulgaris. Eighteen subjects with at least 3% body surface area involvement were enrolled in four dose groups (0.1, 0.3, 1.0, and 5.0 mg per kg). Safety, pharmacokinetics, and clinical response (e.g., Psoriasis Area and Severity Index (PASI)) were monitored at baseline and at specific time points over a 16-wk follow-up period. Anti-IL-12p40 was generally well tolerated. No related serious adverse events or infusion reactions were reported, and most adverse events were mild. IV anti-IL-12p40 yielded linear pharmacokinetics, with a mean terminal half-life of approximately 24 d. Dose-dependent associations with both the rate and extent of clinical response were observed across the four dose groups. Twelve of 18 subjects (67%) achieved at least a 75% improvement in PASI between 8 and 16 wk after study agent administration. Significant and sustained concentration-dependent improvements in psoriatic lesions were observed in most subjects.

Key words: anti-IL-12p40/interleukin-12/interleukin-23/PASI/psoriasis
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Psoriasis vulgaris is one of the most common human skin diseases, affecting 1%–3% of the general population (Greaves and Weinstein, 1995). Psoriasis is a complex disorder, which was initially characterized by inflammation, keratinocyte hyperproliferation, and decreased epidermal differentiation (Christophers and Sterry, 1993). More recently, substantial evidence indicates that T lymphocytes, specifically the type 1 T helper cell (Th1) subtype, macrophages, and certain cytokines play a pivotal role in the pathogenesis of the disease (Barker *et al*, 1991; Boyman *et al*, 2004). The significant role of T cells is demonstrated by the fact that transplantation of bone marrow from a psoriatic donor induces the disease in recipients, whereas transplantation of bone marrow from a non-diseased donor to a recipient with psoriasis is curative (Jowitt and Yin, 1990; Kanamori *et al*, 2002). Furthermore, systemic agents such as cyclosporin A and methotrexate have been known to inhibit T cell function and/or proliferation and suppress psoriatic disease. Although these agents are effective, potential renal, hepatic, and pulmonary toxicity limits their use (Greaves and Weinstein, 1995; Griffiths *et al*, 1995). This has spurred the development of new biologic therapies (i.e., monoclonal antibodies and fusion proteins) that selectively target key cytokines and receptor molecules in the T cell-mediated inflammatory process rather than providing generalized immunosuppression associated with previous therapies (Chaudhari *et al*, 2001; Papp *et al*, 2001; Krueger, 2002; Gordon *et al*, 2003; Gottlieb *et al*, 2003; Lebwohl *et al*, 2003; Leonardi *et al*, 2003).

Two cytokines that are thought to be important in the development of Th1 immune responses in psoriasis are interleukin-12 (IL-12) and IL-23. Both cytokines are produced by antigen-presenting cells, such as macrophages and dendritic cells, and function by activating T cells and natural killer cells. IL-12 and IL-23 are members of a heterodimeric family of soluble cytokines that are comprised of p35/p40 protein subunits in IL-12 and p19/p40 protein subunits in IL-23. The IL-12 p40 subunit of either cytokine will bind to the transmembrane IL-12 receptor β 1 (IL-12Rβ1) that is found on the surface of immune cells.

Abbreviations: Anti-IL-12p40, antibody to interleukin-12 p40 subunit; AUC, area under the curve; BSA, body surface area; C_{max}, maximum serum concentration; ELISA, enzymed-linked immunosorbant assay; IFN, interferon; IL, interleukin; IV, intravenous; LLOQ, lower limit of quantification; PASI, psoriasis area and severity index; PGA, physician's global assessment; $t_{1/2}$, terminal half-life; Th1, type 1 T helper

Subsequent binding of IL-12 p35 or IL-23 p19 to their receptor partners, IL-12Rβ2 and IL-23R, respectively, results in immune signaling events that are specific for each cytokine. Thus, interruption of the IL-12 p40/IL-12Rβ1 interaction will prevent the biological activity of both IL-12 and IL-23. The functions of IL-12 have been well characterized and include induction of interferon-γ (IFN-γ), differentiation of Th1 cells, and bridging between innate resistance and adaptive immunity (Trinchieri, 2003). Although many of the immune consequences of IL-23 are still the subject of active research, IL-23 has been proposed to have functions that are similar, but not identical, to those of IL-12 (Oppmann *et al*, 2000).

A growing body of scientific evidence suggests that both IL-12 and IL-23 may contribute to the underlying pathological processes associated with psoriasis. IL-12 p40 and IFN-γ protein and mRNA are markedly increased in psoriatic skin lesions, but not in adjacent normal skin, and are predominately expressed on mononuclear cells in the dermis (Yawalkar *et al*, 1998). In a study of patients with psoriasis, it was shown that IL-12 p40 and IL-23 p19 gene expression was greatly increased in psoriatic skin lesions, whereas there was no increase in IL-12 p35 expression (Lee *et al*, 2004). In a transgenic mouse that overexpressed IL-12 p40, it was shown that IL-23, but not IL-12, was constitutively produced by basal keratinocytes (Kopp *et al*, 2003). Since keratinocytes are thought to be a key participant in psoriasis pathobiology, IL-23 production may provide a molecular explanation for their involvement. Collectively, these data support the potential contribution of IL-23 to the pathophysiology of psoriasis. A murine model of psoriasis demonstrated the appropriateness of IL-12 and IL-23 as therapeutic targets. A neutralizing antibody to IL-12 p40 successfully abolished psoriatic lesions in mice, even when administered after transfer of the T cell subset that induced the psoriasis-like condition (Hong *et al*, 1999). Therefore, pre-clinical analyses support the clinical investigation of IL-12 and IL-23 neutralization using an antibody to the human interleukin-12 p40 subunit (anti-IL-12p40) in subjects with psoriasis.

Non-clinical toxicology studies with anti-IL-12p40 administered intravenously (IV) or subcutaneously to cynomolgus monkeys have been conducted. Anti-IL-12p40 was administered IV once weekly for a month or subcutaneously twice weekly for 6 mo at doses up to 50 mg per kg. Anti-ILp40 was well tolerated in all of the multi-dose toxicity studies in monkeys given IV or subcutaneous doses up to 50 mg per kg. No overt signs of toxicity were observed. Minimal signs of local irritation were observed in some animals injected with multiple subcutaneous doses of anti-IL12p40. IV and subcutaneous dose embryo-fetal toxicity studies were performed in monkeys to support IV dose administration of anti-IL12p40 to women of childbearing potential. No maternal or fetal abnormalities were observed following doses up to 50 mg per kg administered during the period of organogenesis. An additional study was conducted in a monkey asthma model to determine if administration of anti-IL-12 would exacerbate induced asthmatic effects. Results showed that anti-IL-12p40 did not exacerbate the pulmonary function of the study monkeys following two IV 50 mg per kg doses administered 4 wk apart.

Anti-IL12p40 is a human IgG1 κ monoclonal antibody that binds to the p40 subunit of human IL-12 and IL-23 and prevents its interaction with IL-12Rβ1. Therefore, anti-IL-12p40 neutralizes IL-12 bioactivity, as measured by the inhibition of IFN-γ production from mitogen-stimulated CD3+ T-lymphocytes (Brok *et al*, 2002; Cua *et al*, 2003). *In vivo* administration of anti-IL-12p40 inhibited the development of neurologic dysfunction and neuropathological changes in a marmoset model for multiple sclerosis, which like psoriasis, is considered to be a Th1-associated autoimmune disease with a strong contribution from IL-12 and IL-23 (Brok *et al*, 2002). Therefore, the potential therapeutic activity of anti-IL-12p40 that had been established *in vitro* and *in vivo* warranted a first-in-human investigation in a psoriasis population. The primary objectives of this phase I study were to evaluate the short-term safety, assess the pharmacokinetics, and determine the clinical response of single, ascending, IV administrations of anti-IL-12p40 in subjects with moderate-to-severe psoriasis vulgaris.

Results

Demographic and baseline disease characteristics The demographic and baseline disease characteristics for the study population are shown in Table I. All 18 subjects who participated in the study were evaluable, having received the scheduled single-dose infusion of anti-IL-12p40 and completed the scheduled follow-up visits; no subject discontinued study agent infusion. The dose groups were comparable with respect to demographics and baseline disease characteristics. A predominance of men (14 of 18 subjects; 78%) enrolled in the study, primarily because of the exclusion of women of childbearing potential. The dose groups were generally comparable in relation to the duration and extent of disease, considering the small number of subjects in each group. The minimal duration of psoriasis was 3.4 y, with a mean duration range of 13.6–19.7 y across the four dose groups. Baseline BSA of plaque psoriasis involvement ranged from 3.0% to 35.0%, and baseline PASI ranged from 5.6 to 34.8.

Safety No treatment-related serious adverse events were reported. One subject in the 5.0 mg per kg dose group experienced a serious adverse event that the investigator considered not related to study drug. This subject had a pre-existing disc disease and had undergone laminectomy and partial discectomy approximately 6 mo before receiving study agent. The back pain worsened approximately 11 wk after receiving study agent, and an additional laminectomy and discectomy was performed approximately 2 wk later. This event was continuing at the end of the study.

All subjects experienced at least one adverse event during the 16-wk study, but there was no evidence of a relationship between dose and response in intensity, duration, or frequency of adverse events. The majority of adverse events were mild in intensity. There were no adverse events suggestive of infusion reactions or immediate or delayed hypersensitivity responses to the study drug. No adverse events resulted in either discontinuation or reduction in the dose of the study agent. The most commonly reported

Table I. Demographics

	Dose groups (mg per kg)			
	0.1	**0.3**	**1.0**	**5.0**
Number of subjects	4	4	5	5
Age (years)				
Mean	37.5	40.0	42.8	42.8
Range	23–51	30–52	32–54	31–55
Gender				
Male	4	2	5	3
Female	0	2	0	2
Weight (kg)				
Mean	95.3	93.2	99.4	84.6
Range	69.1–140.5	70.0–127.3	68.9–110.9	65.5–131.8
Baseline PASI				
Median	11.0	18.2	14.7	13.6
Range	5.8–13.1	8.8–34.8	7.4–15.8	5.6–27.8
% BSA				
Mean	10.9	15.0	9.4	11.6
Range	6.5–15	7.0–20.0	4.0–16.0	3.0–35.0
Duration of psoriasis (years)				
Mean	13.6	16.9	16.6	19.7
Range	3.4–20.2	11.5–25.2	7.6–30.8	9.0–42.0

PASI, psoriasis area and severity index; BSA, body surface area.

adverse events included decreases in T-lymphocyte subsets (10 subjects), headache (six subjects), common cold symptoms (five subjects), and pain at the biopsy site (four subjects). The majority of specific adverse events occurred in only one or two of the 18 subjects.

The majority of adverse events were not considered to be related to study agent by the investigators; however, because of the potential role of IL-12 in Th1 differentiation and natural killer cell cytolytic activity, asymptomatic decreases in the counts of CD4+ (the surface marker for T helper cells) or CD16+/CD56+ (natural killer cells) were identified by the investigators as adverse events considered probably or definitely related to study agent administration (Abbas *et al*, 2000). Transient decreases in the numbers of CD4+ and CD16+/56+ cells were observed in some subjects, but the degree and duration of such decreases were highly variable across the four dose groups (Fig 1). A decrease in the number of CD4+ cells was observed in some subjects between 24 and 72 h after study agent administration, with a return to baseline levels between 1 and 12 wk after study drug administration. In two subjects, the CD4+ counts were below 400 cells per mm^3 for a period of 5 d, with nadirs of 369 and 356 cells per mm^3, respectively. No relationship between decreases in either CD4+ or CD16+/56+ cells and dose was observed and no variations in the numbers of CD3+, CD19+, CD8+, or CD4+/CD8+ populations were detected.

The long half-life of anti-IL-12p40 limited the extent to which the development of antibodies to the anti-IL-12p40 could be evaluated in this study. Of the 18 enrolled subjects, however, one subject (0.1 mg per kg dose group) demonstrated a 1:80 titer at 16 wk after study agent administration. The antibodies were specific for the study agent, since preincubation of the serum with the anti-IL12p40 completely neutralized the assay reactivity. The development of antibodies to anti-IL-12p40 in this subject was not associated with any adverse events likely to be related to the immune response. Another subject (0.1 mg per kg dose group) was confirmed to be negative for antibodies to study agent. Antibody determinations were considered inconclusive in the remaining 16 subjects because anti-IL-12p40, which interferes with the *in vitro* assay, was present in all post-dose serum specimens.

Pharmacokinetics The mean serum concentration–time profiles of anti-IL-12p40 are shown for each treatment group in Fig 2. Anti-IL-12p40 demonstrated linear pharmacokinetics over the dose range evaluated. Dose-proportional increases in maximum serum concentration (C_{max}) were observed. Across the four dose groups, the C_{max} (mean $\pm$ SD) ranged from 3.0 ± 0.6 μg per mL (0.1 mg per kg dose group) to 152.0 ± 19.1 μg per mL (5.0 mg per kg dose group). The $t_{1/2}$ (mean $\pm$ SD) was 27.0 ± 7.5, 18.5 ± 3.6, 25.9 ± 3.7, and 23.7 ± 5.7 d in the 0.1, 0.3, 1.0, and 5.0 mg per kg, dose groups respectively, indicating similar elimination rates with all doses. The AUC (mean $\pm$ SD) increased linearly with the dose, ranging from 53.6 ± 8.9 μg·d per mL in the 0.1 mg per kg dose group to 2607.5 ± 398.9 μg·d per mL in the 5.0 mg per kg dose group.

Clinical response The clinical response profile, as measured by the change in PASI from baseline, for the four anti-IL-12p40 dose groups is shown in Fig 3. In the 0.1 mg per kg group, three of four subjects (75%) reported at least a 50% improvement in PASI by week 8 (Fig 3*A*). One of these subjects (25%) achieved at least a 75% reduction in PASI score by week 8, a response that was maintained through week 16. In the 0.3 mg per kg dose group, two of four subjects (50%) exhibited at least a 75% reduction in PASI score by week 12 (Fig 3*B*), which was sustained through week 16; however, the two subjects in the 0.3 mg per kg dose group who had the highest baseline PASI scores (i.e., 21.3 and 34.8) did not exhibit a significant clearing in their psoriatic plaques. In the 1.0 mg per kg dose group, all five subjects (100%) achieved at least a 50% improvement in PASI score by week 8. Three of five subjects (60%) and four of five subjects (80%) reported a minimum or greater than 75% reduction in PASI score by weeks 12 and 16, respectively (Fig 3*C*). In the 5.0 mg per kg group, three of five subjects (60%) reported at least a 50% improvement in PASI at week 4, with one subject achieving at least a 75% improvement. All five subjects (100%) achieved at least a 75% reduction in PASI score by week 12, a response that was sustained through week 16 (Fig 3*D*). Figure 4 shows psoriasis activity before and at various time points after

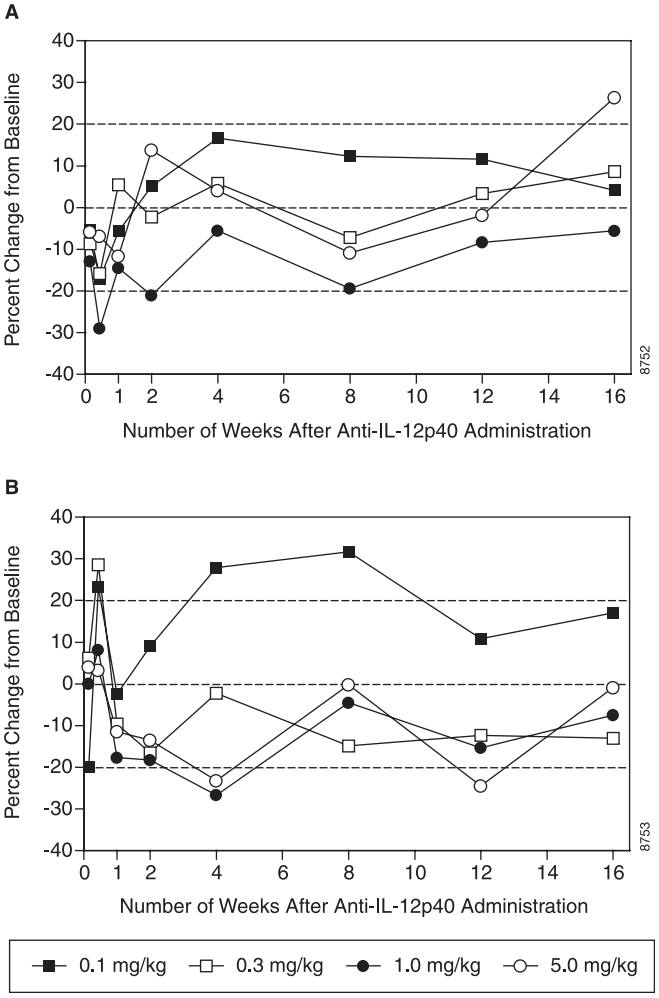

Figure 1
Percent change from baseline CD4+ and CD16+/56+ cell counts. The mean percent from baseline CD4+ (*A*) and CD16+/56+ (*B*) peripheral blood cell counts for each dose group are plotted over the 16 wk evaluation period. (■) 0.1 mg per kg dose group; (□) 0.3 mg per kg dose group; (●) 1.0 mg per kg dose group; (○) 5.0 mg per kg dose group.

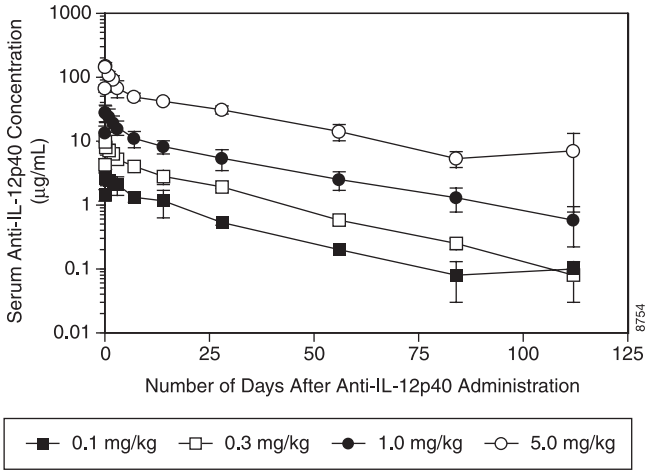

Figure 2
Mean (± SD) serum concentration *versus* time profiles of the antibody to interleukin-12 p40 subunit (anti-IL-12p40) antibody following single intravenous infusions. (■) 0.1 mg per kg dose group; (□) 0.3 mg per kg dose group; (●) 1.0 mg per kg dose group; (○) 5.0 mg per kg dose group.

treatment with anti-IL-12p40 in subjects from different dose groups.

Results for clinical response as measured by PGA scores showed that, by week 2, at least one subject in each treatment group achieved mild or better PGA scores. All subjects in the 1.0 and 5.0 mg per kg groups achieved mild or better PGA scores at weeks 12 and 16 compared with 75.0% and 50.0% of subjects in the 0.1 and 0.3 mg per kg groups, respectively, at both of these time points. The relative improvement in PASI and PGA scores for each dose group is shown in Table II. At week 16, a clear correlation was observed between the anti-IL-12p40 dose and the proportion of subjects achieving at least a 75% improvement in PASI score or a minimal or better PGA score, both of which are indicative of clinically meaningful improvement.

Discussion

The purpose of this phase I clinical trial was to determine the short-term safety, pharmacokinetics, and clinical response of anti-IL-12p40 in subjects with moderate-to-severe plaque psoriasis. The majority of subjects in this study had a long history of disease, with the mean duration ranging from 13.6 to 19.7 y across treatment groups. Subjects were administered single IV doses of anti-IL-12p40, ranging from 0.1 to 5.0 mg per kg, which spanned an estimated subtherapeutic to therapeutic concentration range. This range was derived from *in vitro* and animal studies that included careful evaluation of toxicity and efficacy.

This study demonstrated that single IV administrations of anti-IL-12p40 at different doses were well tolerated in subjects with moderate-to-severe plaque psoriasis. No treatment-related serious adverse events or adverse events requiring discontinuation or dose reduction were reported in the study. Most adverse events were mild in severity and considered not related to study agent administration by investigators. No dose–response with relation to the intensity, duration, or frequency of any adverse event was apparent. No adverse events suggestive of infusion reactions and no immediate or delayed hypersensitivity responses to study agent were reported. Transient decreases in peripheral CD4+ and CD16+/56+ cells were observed in some subjects after a single IV administration of study drug, but values for these parameters were highly variable over time and dose and did not correlate with any clinical symptoms.

Pharmacokinetic evaluations following IV administration of a single IV dose of anti-IL-12p40, ranging from 0.1 to 5.0 mg per kg, yielded linear pharmacokinetics, with a mean terminal half-life ($t_{1/2}$) of approximately 24 d and a dose-proportional increase in the C_{max} and systemic exposure (AUC) of anti-IL-12p40.

Of the 18 subjects tested, immunogenicity status (i.e., development of antibodies to IL-12 p40) was inconclusive in 16 subjects and negative and positive in one subject each (both 0.1 mg per kg) at 16 wk following study agent infusion. The immune response was specific for anti-IL-12p40, as characterized by complete neutralization of immune response activity in the enzyme-linked immunosorbent assay

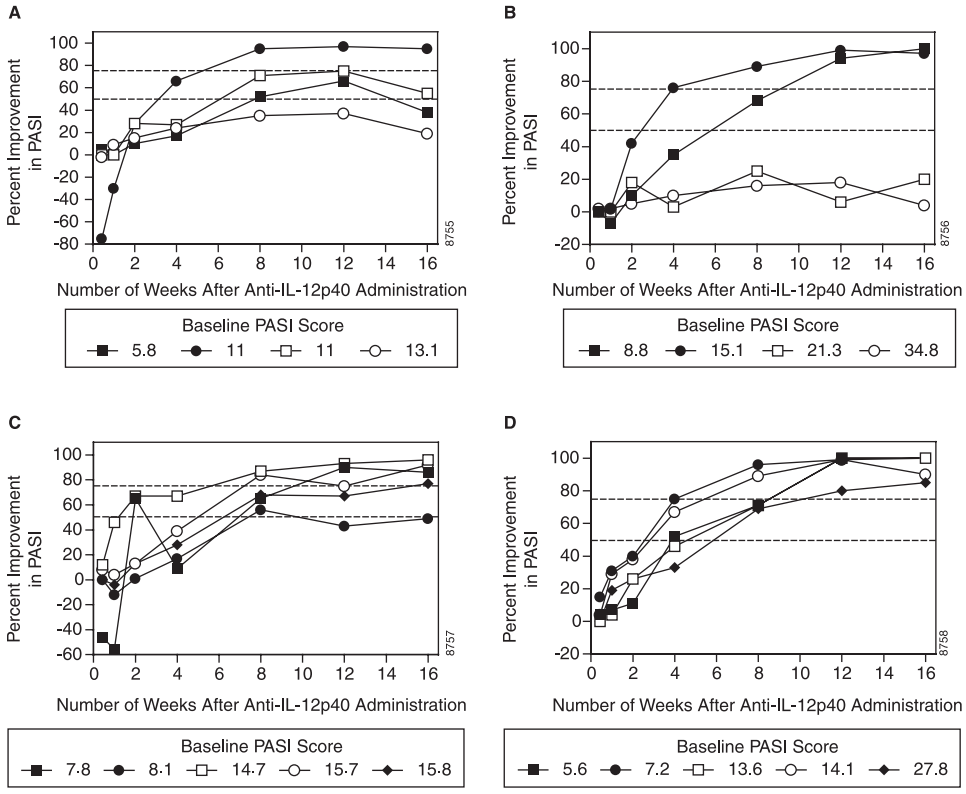

Figure 3
Percent improvement in baseline psoriasis area and severity index (PASI) scores. The percent improvement in PASI score for each subject within a dose group is plotted over the 16 wk evaluation period. (*A*) 0.1 mg per kg dose group; (*B*) 0.3 mg per kg dose group; (*C*) 1.0 mg per kg dose group; (*D*) 5.0 mg per kg dose group. For reference, the baseline PASI scores for each subject within a dose group is shown below each graph.

(ELISA) following pre-incubation of the serum sample with excess anti-IL-12p40. The clearance rate of anti-IL-12p40 for the individual who tested positive was similar to that for other subjects in the same dose group. Although the consistent elimination rate of anti-IL-12p40 in nearly all subjects suggests the absence of a significant immune response, the high number of inconclusive determinations precludes making any firm conclusion about the antigenicity of IV anti-IL-12p40.

The significant and sustained concentration-dependent improvements in psoriasis were consistent across two clinical response measurements (PASI and PGA) and were observed in the majority of subjects, which supports the efficacy of anti-IL-12p40 in psoriasis. Overall, 83% and 67% of subjects, respectively, exhibited at least a 50% and 75% improvement in PASI score during the 16-wk evaluation period. All 10 subjects in the 1.0 and 5.0 mg per kg groups and two subjects each in the 0.1 and 0.3 mg per kg groups achieved PGA scores of minimal or better by week 16. The 0.3 mg per kg dose may have been subtherapeutic in the two subjects with the more severe disease (baseline PASI scores of 21.3 and 34.8) who did not exhibit significant clearing by week 16, as further shown by the subject with the highest baseline PASI score (27.8) in the 5.0 mg per kg group who achieved clearing at the higher dose. Concentration-dependent improvements in both the rate and extent of therapeutic benefit were observed across the four dose groups. Noticeable clearing of psoriatic plaques was observed as early as 2 wk following study agent administration, with maximal therapeutic benefit achieved at 12 wk for the majority of subjects. In addition, therapeutic benefit was sustained throughout the 16-wk evaluation period in subjects who achieved at least a 75% improvement in PASI scores.

This is the first report of human data suggesting that IL-12 p40 is an appropriate therapeutic target for subjects with psoriasis. IL-12 p40 and IL-23 p19 gene expression has been reported in psoriatic plaques (Yawalkar *et al*, 1998; Lee *et al*, 2004), and data from murine models has suggested that neutralization of IL-12 or IL-23 would provide therapeutic benefit (Hong *et al*, 1999; Kopp *et al*, 2003). The results presented here, however, are the first to suggest that neutralization of IL-12 and IL-23 through a fully human monoclonal antibody to IL-12 p40 provides clinical benefit in human psoriasis. These results support the strategy of developing monoclonal antibodies targeted at key cytokines involved in the development of the Th1 immune response in autoimmune diseases, such as anti-IL-12p40 in the case of psoriasis. Furthermore, these results confirm that the p40 subunit of IL-12 is involved in the underlying pathogenesis of psoriasis and that developing a monoclonal antibody to directly target this subunit contributes to the effectiveness of this biologic.

This study was limited by certain factors related to study design, subject population, and sampling difficulties. The study design was open label and lacked a placebo group, and thus, did not allow a blinded and comparative assessment of clinical response. Furthermore, because this was a first-in-human study, more subjects with less severe psoriasis were allowed than would typically be recruited in Phase II/III studies of biological therapy. The determination of immunogenicity was limited in this study because of the presence of study agent in the circulation of most subjects throughout the evaluation period. Finally, the small number of subjects allows only limited early assumptions about the safety of anti-IL-12p40.

In conclusion, this clinical study provides the first information on the safety, pharmacokinetics, and clinical

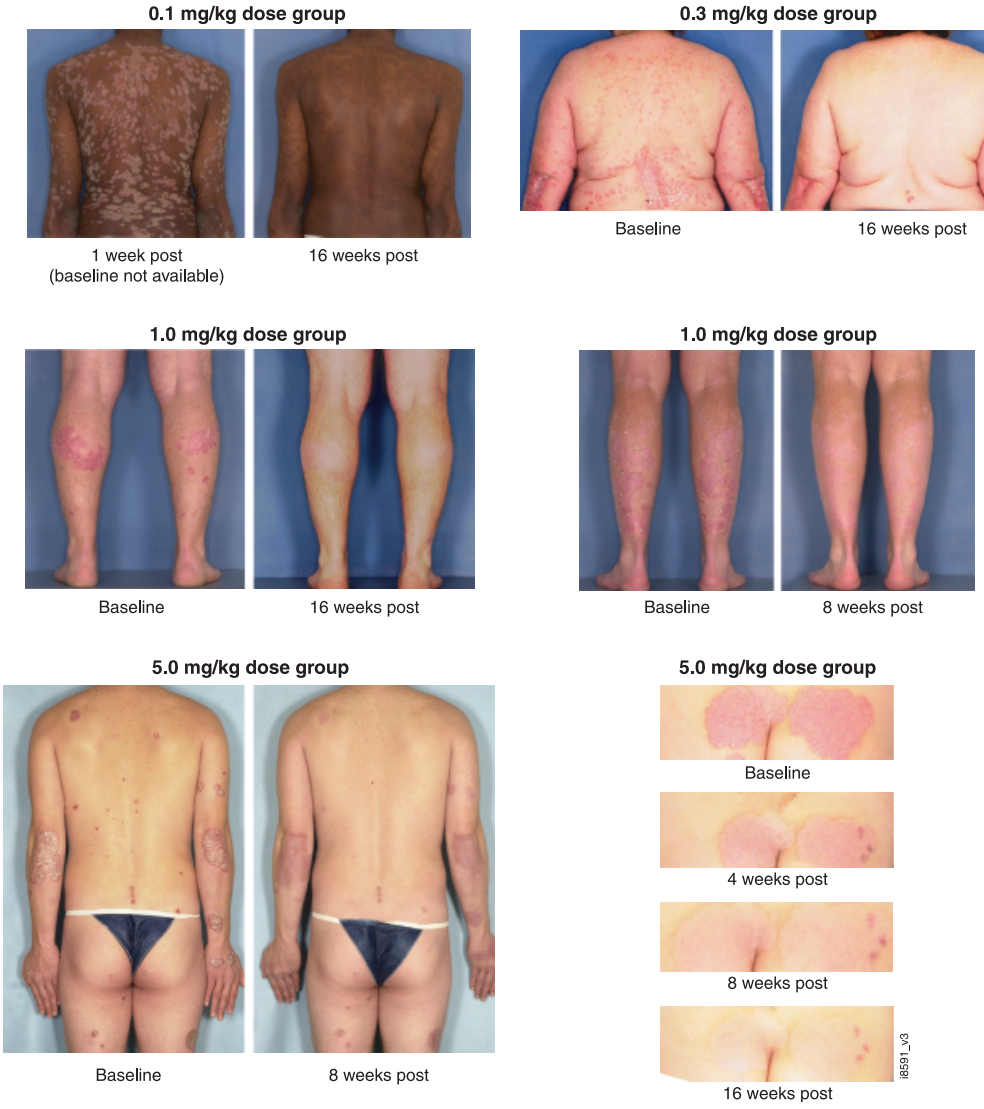

Figure 4
Psoriasis activity before and after treatment with antibody to interleukin-12 p40 subunit. 0.1 mg per kg dose (1 wk post-treatment [*baseline not available*] and 16 wk post-treatment); 0.3 mg per kg dose (baseline and 16 wk post-treatment); 1.0 mg per kg dose (baseline and 16 wk post-treatment); 1.0 mg per kg (baseline and 8 wk post-treatment); 5.0 mg per kg dose (baseline and 8 wk post-treatment); 5.0 mg per kg (baseline, and 4, 8 and 16 wk post-treatment).

Table II. Improvement in PASI and PGA scores through week 16

Dose group	Number of subjects achieving at least a 75% improvement in PASI score	Number of subjects achieving minimal or better PGA score
0.1 mg per kg (n = 4)	1	2
0.3 mg per kg (n = 4)	2	2
1.0 mg per kg (n = 5)	4	3
5.0 mg per kg (n = 5)	5	4

PASI, psoriasis area and severity index; PGA, physician's global assessment.

response of single IV administrations of anti-IL-12p40 in human subjects with moderate-to-severe plaque psoriasis. Anti-IL-12p40 was well tolerated, with no significant safety concerns, and demonstrated substantial concentration-dependent efficacy. Further evaluation is merited in larger, randomized, and blinded clinical studies.

Materials and Methods

Study protocol and subject eligibility This clinical study was conducted at two sites; the PAREXEL-Baltimore Clinical Pharmacology Research Unit and the Clinical Research Center at the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School. Institutional Review Boards at both sites approved the study, which was conducted in conformance with the regulations established for the Protection of Human Subjects (21 Code of Federal Regulations Part 50) and Institutional Review Boards (21 Code of Federal Regulations Part 56), in accordance with Good Clinical Practices, and in compliance with local regulations. Subjects were recruited through general advertising, and all subjects provided written informed consent prior to the performance of any study-specific procedures.

Men and women in general good health and between the ages of 18 and 65 y were eligible to participate in this study. Female subjects were either postmenopausal (no menstrual period for a minimum of 1 y) or surgically sterilized; subjects were required to have a negative serum pregnancy test at study entry. To minimize the possibility of indirect exposure to anti-IL-12p40, male subjects agreed to use adequate contraceptives during the study and for 6 mo after study drug administration. Subjects had chronic moderate-to-severe plaque psoriasis involving at least 3% body surface area (BSA) and at least two plaques located on either the trunk or extremities, with a confirmed diagnosis at least 6 mo prior to

screening. In an effort to expedite study enrollment, the study protocol was amended to decrease the original study entry criteria of at least 5% BSA of plaque psoriasis involvement to at least 3% BSA.

A chest X-ray was required within 1 y of study agent administration to exclude subjects with malignancy, infection, fibrosis, or past/current tuberculosis infection.

Subjects were excluded from participating in the study if they had any serious systemic or local infection within 3 mo before screening, a history or any signs of lymphoproliferative disease, or a known malignancy or a history of malignancy within the previous 5 y (with the exception of basal cell or squamous cell carcinoma of the skin that had been fully excised with no evidence of recurrence). Participants had to have a medical history negative for alcohol or substance abuse within the previous 6 mo and had to have negative test results for HIV, hepatitis B, hepatitis C prior to enrollment.

Subjects could not have received previous treatment with monoclonal antibodies or antibody fragments or any previous treatment with a non-monoclonal antibody/non-immunoglobulin investigational drug within 28 d prior to infusion of study agent. All systemic psoriasis medications, including psoralen long-wave ultraviolet radiation treatments, or other systemic immunosuppressives were prohibited within 4 wk before the study drug administration. The use of single-treatment phototherapy (ultraviolet B or self-treatment with tanning beds) was not allowed within 14 d prior to the study drug administration and the use of topical therapy for psoriasis was prohibited within 7 d prior to the study agent administration. The only medications allowed during the study were lipid-lowering drugs, anti-hypertensives, oral medications for type II diabetes, estrogen replacement therapy, thyroid replacement therapy, antihistamines used for pruritus, antacids, histamine H2-receptor antagonists, and proton pump inhibitors; subjects taking these medications were required to have been on chronic stable doses prior to screening.

The study was a phase I, first-in-human, non-randomized, open-label, single administration, dose-escalating study of anti-IL-12p40, designed to evaluate the safety, pharmacokinetics, and clinical response in subjects with moderate-to-severe psoriasis. Each subject received a single IV infusion of study drug. The dose groups were as follows: 0.1 mg per kg ($n = 4$), 0.3 mg per kg ($n = 4$), 1.0 mg per kg ($n = 5$), and 5.0 mg per kg ($n = 5$). For each subject, anti-IL-12p40 was administered by infusion over a minimum of 120 min. As a safety precaution, subsequent subjects within each dose group were not administered anti-IL-12p40 for at least 48 h after the first subject had received the study medication. The duration of safety follow-up for each subject was 16 wk after administration of the study agent.

Study procedures

Safety assessments The safety and tolerability of anti-IL-12p40 were assessed by monitoring the occurrence of adverse events or abnormalities identified by standard laboratory tests, vital sign measurements, and physical examinations. Laboratory tests performed at each visit included complete blood count with differential and platelet count, lymphocyte subset analyses, serum chemistries, prothrombin time, and partial thromboplastin time. Lymphocyte subset analyses and other laboratory tests were performed using standard methodology at MedStar Research Institute (Washington, District of Columbia). To ensure reliable test results, study personnel were given specific instructions for sample handling.

Assessments of antibody production to anti-IL-12p40 Serum samples for immune response assessments were obtained prior to infusion and at 2, 8, and 16 wk after infusion of the study agent, anti-IL12p40. The development of an antibody response to anti-IL-12p40 was measured using an antigen bridging enzyme immunoassay in which serum samples were added to an anti-IL-12p40-coated plate. Antibodies in the serum that bind to anti-IL-12p40 were then detected by adding exogenous study agent that was previously biotinylated anti-IL-12p40. Thus, samples that contain antibodies to anti-IL-12p40 will be detected by streptavidin reactivity. Subjects were designated immune response positive if antibodies to study agent were detected at any time point following infusion. Subjects were designated as immune response negative if they did not demonstrate antibodies to anti-IL-12p40 at any time point following infusion and if the study agent was not detectable in serum. If subjects had no response in the antigen bridging assay, yet had measurable levels of anti-IL-12p40 in their serum, they were designated as immune-response inconclusive. The presence of study agent in the antigen-bridging assay characteristically interferes with the detection of an antibody immune response because both arms of the immunoglobulin must be available to bind the antigen coated on the plate, as well as the streptavidin-conjugated antigen.

Pharmacokinetic assessments Serum samples for pharmacokinetic assessments were obtained at baseline, 1 h after the start of infusion, at the end of infusion (2 h), and at 4, 24, 48, and 72 h after the start of infusion of the study agent. Subsequent serum samples were collected at 1, 2, 4, 8, 12, and 16 wk following the study agent administration. Serum anti-IL-12p40 levels were measured using a validated ELISA with a lower limit of quantification (LLOQ) of 0.1 μg per mL following a 10-fold dilution. Pharmacokinetic parameters, including C_{max}, $t_{1/2}$, and AUC, were derived from non-compartmental analysis.

Clinical response assessments Clinical response measurements (PASI and PGA), were performed at baseline, 72 h, and at 1, 2, 4, 8, 12, and 16 wk after administration of study agent. PASI, a system used for grading the severity of psoriatic lesions and their response to therapy, produces a numeric score ranging from 0 to 72 based on the rating of erythema, thickness, and scaling on the head, trunk, and upper and lower extremities (Fredriksson and Pettersson, 1978). PGA is an overall assessment of a patient's psoriasis, based on four signs of disease (severity, thickness, scaling, and erythema) as rated on a scale of 0–5. To reduce inter-rater variability, every effort was made to avoid having more than one assessor perform the PASI and PGA measurements for each subject. To complement PASI and PGA assessments, digital images were collected for all subjects enrolled in the study. Multiple predefined views were collected with variables, such as lighting, framing, background, exposure, and reproduction ratios, held constant to ensure that the skin was the only variable changing within the image over time. Although pharmacodynamic measurements were performed on biopsied tissue from designated target lesions, the pharmacodynamic results are not presented in this paper.

Statistical methods Because this was a phase I, first-in-human, non-randomized, open-label study, no interim analysis or formal hypothesis testing was conducted and no formal sample size determinations were undertaken. The sample size was small because the study was conducted to provide preliminary safety assessments of single infusion regimens of anti-IL-12p40. Continuous variables were summarized using descriptive statistics (e.g., number of observations, means, medians, standard deviations, and ranges) and discrete variables were summarized using frequencies and percentages.

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