

# Long-term safety profile of sipilizumab, a humanized anti-CD2 monoclonal antibody, in subjects with chronic plaque psoriasis

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## Abstract

**Background:** Prolonged depletion of activated T cells via targeted therapy may reduce disease activity in chronic plaque psoriasis, but may potentially lead to increased risk of serious infection. **Objectives:** To evaluate the long-term safety profile of sipilizumab, an anti-CD2 monoclonal antibody, in chronic plaque psoriasis subjects who experienced persistent sipilizumab-induced lymphocyte depletion. **Methods:** Subjects (n=94) with absolute lymphocyte counts (ALC) >30% lower than baseline or absolute CD4 count <250 cells/ $\mu$ L post-sipilizumab treatment were followed prospectively for up to 5.25 years from last sipilizumab dose for occurrence of selected medically important events: infection, malignancy, and autoimmune diseases. **Results:** Five selected medical events were reported: cholecystitis, colitis, myelofibrosis, encephalitis, and bronchitis; first three met serious adverse event criteria, none were considered sipilizumab-related. Repletion of ALC to normal levels occurred in 53% of subjects within 2 years after treatment cessation. **Conclusion:** Preselected medically important events were uncommon in subjects with sipilizumab-induced lymphocyte depletion.

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## INTRODUCTION

Psoriasis is a chronic autoimmune skin disease characterized by infiltration of T lymphocytes into the dermis and epidermis and abnormal proliferation of keratinocytes. <sup>1</sup> Biological agents targeting tumor necrosis factor-alpha, CD-23, CD11a, and the p40 component of interleukin-12 and interleukin-23 in chronic plaque psoriasis all provide efficacy associated with target-specific safety risks that may include an increased risk of infection related to immunosuppression. Sipilizumab (MedImmune, LLC, Gaithersburg, MD) is a 150 kDa humanized IgG monoclonal antibody that specifically targets the CD2 receptor on T lymphocytes and natural killer (NK) cells. CD2 is a costimulatory molecule for antigen-specific lymphocyte activation that mediates the adhesion between activated T cells and antigen-presenting cells or NK cells and target cells. Sipilizumab may suppress the function of T cells and NK cells or eliminate them from the circulation. <sup>2</sup>

A total of 615 psoriasis subjects received sipilizumab in Phase 1 and 2 studies. In these studies, evidence of significant clinical efficacy was not observed at the doses

tested. <sup>3</sup> A subset of these subjects (227/615, 37%) experienced persistent dose-dependent reductions in absolute lymphocyte counts (ALC), CD4+, or CD8+ T cells at their final study visit. The aim of the current study was to conduct a long-term safety profile follow-up of those subjects and characterize their lymphocyte repletion to determine whether they were at increased risk of serious long-term complications.

## SUBJECTS AND METHODS

Subjects who had previously completed participation in a clinical study of psoriasis in which they received sipilizumab and who had an ALC more than 30% lower than baseline (defined as baseline prior to any sipilizumab exposure) or an absolute CD4 count of less than 250 cells/ $\mu$ L at their final visit were eligible to participate in this prospective, long-term observational safety profile study.

## STUDY DESIGN

Subjects with chronic plaque psoriasis were eligible to participate in the study if they had previously completed participation in one of six Phase 1 or Phase 2 trials in which they received sipilizumab and had either a decrease of >30%

in ALC compared to baseline levels (ie, prior to any sipilizumab exposure) or an absolute CD4 count of <250 cells/ $\mu$ L at their final study visit. Subjects were followed for 2 years (ie, through study day 720). Subjects who continued to have either a decrease of >30% in ALC compared to baseline or an absolute CD4 count of < 250 cells/ $\mu$ L at study day 720, were eligible for an additional 2 years of follow up, which corresponded to up to 5.25 years from the last sipilizumab dose. No study drug was administered during the current study.

Follow-up clinic visits occurred every 3 months for 4 years. At each visit, selected medical events, concomitant medications, complete blood cell count (CBC) with differential and platelet count, and lymphocyte flow cytometry for CD3+, CD4+, and CD8+ cells were assessed. Serum samples for measurement of anti-siplizumab antibodies were collected on study days 0, 90, 180, 360, 540, and 720 and every 6 months thereafter through year 4. The study protocol (ClinicalTrials.gov registration number NCT00131066) was approved by the institutional review boards of the participating study sites, and all subjects signed a written informed consent before study-related procedures were performed.

The primary objective of the study was to monitor the long-term safety and lymphocyte repletion profiles of subjects with psoriasis who participated in a study in which they received sipilizumab and exhibited persistent lymphopenia. Safety endpoints included selected medical events of: infections, including those resulting in treatment with intravenous antibiotic, antiviral, or anti-fungal therapies, mycobacterial infection, *Pneumocystis carinii* pneumonia, and human immunodeficiency virus infection and other acquired immunodeficiency conditions; malignancy; and autoimmune disease, excluding psoriasis. Selected medical events that met criteria for a serious adverse event (SAE) were also classified as such. SAEs were described by body system and Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART), severity, and relationship to study drug. Other endpoints included ALC, CD3+, CD4+, and CD8+ cells in blood and numbers and percentages of subjects with an ALC >30% lower than their baseline and/or an absolute CD4 count <250 cells/ $\mu$ L. The secondary objective of this study was to evaluate the development and durability of anti-siplizumab antibodies.

## STATISTICS

Descriptive statistics, including mean, median, standard

deviation, and range, were used to analyze continuous variables. Categorical data were summarized by the number and percentage of subjects in each category. Data were summarized by study day and by years from last sipilizumab dose.

## RESULTS

Of the 227 subjects eligible to participate in this study, 94 were enrolled at 31 sites in the USA, Canada, Belgium, France, Germany, and the Netherlands. Fifty-seven (61%) subjects were male, the mean  $\pm$  SD age was 43.7  $\pm$  12.0 years, the mean  $\pm$  SD weight was 86.1  $\pm$  22.1 kg, and 85 (90%) subjects were white/non-Hispanic. All but 2 subjects had received multiple doses of sipilizumab, ranging from 0.012 mg/kg administered intravenously every 1-2 weeks for 8 doses to 5 mg/kg administered subcutaneously for 16 doses; 78 (83%) of subjects received a dose level of at least 3 mg/kg sipilizumab and 61 (65%) of subjects received at least 6 doses of sipilizumab. The mean  $\pm$  SD total dose of sipilizumab received by subjects was 34.4  $\pm$  18 mg.

Seventy-three (77.7%) subjects completed the study through study day 720. Of the 21 (22.3%) subjects who did not complete the study through study day 720, 8 were lost to follow-up and 13 withdrew consent. At the completion of the 2-year follow-up (day 720), 36 subjects continued to exhibit lymphocyte depletion and therefore were eligible for the additional 2 years safety follow-up. However, no subject completed the study through year 4; 2 subjects withdrew consent, and the remaining 34 subjects stopped the study after the sponsor terminated the clinical trial.

Five selected medical important events were reported in five (5.3%) subjects in this study, one each of cholecystitis, colitis, myelofibrosis, encephalitis, and bronchitis. The cholecystitis, colitis, and myelofibrosis episodes were considered SAEs, and none were attributed to sipilizumab.

A gradual reduction in the proportion of subjects with ALC >30% below their baseline was seen throughout the follow-up period (Figure 1). Normalization of CD4+ cells was faster than ALC repletion; at 1-year follow up, low CD4 counts persisted only in 11% (6/54) of subjects present in the study (Figure 1). The proportion of subjects who had both an ALC >30% lower than baseline and an absolute CD4 count <250 cells/ $\mu$ L progressively decreased during the first year following the final dose of sipilizumab. A low incidence was maintained throughout the rest of the study. A gradual increase in mean total CD3+, CD4+ and CD8+ cells was

seen during follow-up.

Figure 1: Proportion of subjects with ALC less than 30% baseline value prior to sipilizumab (squares) and CD4+ cells less than 250 cells/ $\mu$ L (circles) at 6-month time intervals from study day 0 through 4 years after last dose of sipilizumab. The total number of subjects at each time point is indicated. CBC with differential and lymphocyte flow cytometry were performed at a licensed, central clinical laboratory.

Anti-sipilizumab antibodies were detected in 2 of 91 subjects (2.2%) with adequate blood samples. Both subjects had exhibited anti-sipilizumab antibodies in previous sipilizumab studies.

## DISCUSSION

Of the 615 psoriasis subjects who received sipilizumab during Phase 1 and 2 clinical studies, 227 subjects (37%) exhibited persistent reductions in ALC, defined as an ALC >30% lower than baseline (prior to any sipilizumab exposure), or an absolute CD4 count of <250 cells/ $\mu$ L, at their final visit. The present study was conducted to assess the long-term safety profile of these subjects and to follow up on their lymphocyte repletion. No selected SAEs (infections, malignancies, and autoimmune diseases) were attributable to sipilizumab during the long-term, post-treatment, follow up. After 2 years of follow-up from last sipilizumab dose, the number of subjects with persistent reductions in ALC decreased from 90% (84/93) to 47% (37/78). By 4 years of follow-up, sustained reductions in ALC persisted in 34% (12/35) of subjects.

Based on these data, the Safety Monitoring Committee considered that these subjects were not at an increased risk of serious long-term safety events related to sipilizumab therapy, and recommended an early termination of this study.

Alefacept is a human leukocyte-function-associated antigen type 3 (LFA-3)-IgG1 fusion protein that has a related mechanism of action to that of sipilizumab—it inhibits T-cell activation by blocking the interaction between CD2 and its ligand LFA-3. Alefacept has been shown to induce dose-dependent reductions in circulating total lymphocytes, and CD4+ and CD8+ T lymphocyte counts in patients with chronic plaque psoriasis.<sup>45</sup> During alefacept dosing, the mean maximum reductions from baseline in circulating total lymphocyte counts varied between 33% and 41%.<sup>5</sup> Lymphocyte repletion profile at 3 months post-alefacept

therapy showed that CD4+ T lymphocyte counts increased by about 30% compared to their lowest levels at the end of alefacept therapy.<sup>5</sup> A direct comparison between alefacept and sipilizumab immunosuppressive effects is not possible because of differences in trial design, subjects, and measurement of lymphocyte depletion and repletion at different time points. While a correlation between the magnitude of the reduction in the absolute number of circulating CD4+ and CD8+ memory T-cells and clinical response has been reported for alefacept,<sup>5</sup> such relationship has not been demonstrated for sipilizumab.

The SAEs reported in our study may represent the complications or comorbidities occurring in the general psoriasis population. Colitis, a SAE reported in this study, is a disease that has been associated with psoriasis.<sup>6</sup> Cholecystitis, one of the SAEs reported during our study, was also reported during alefacept long-term studies.<sup>7</sup>

The present study demonstrates that the sustained lymphocyte depletion observed in some subjects treated with sipilizumab has no apparent serious long-term safety consequences during follow-up of up to 5.25 years from final sipilizumab dose.

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