Patent Right	Date	August 7, 2024	Court	Intellectual Property High Court, Fourth Division
	Case number	2023 (Gyo-Ke) 10019		
- A case in which, with regard to the patent for an invention titled "Method for treating atopic dermatitis by administering an IL-4R antagonist," the court ruled that none of the grounds for rescission of the JPO decision, i.e., lack of an inventive step, violation of the support requirement, and violation of the enablement requirement, can be found.				

Case type: Rescission of Trial Decision to Maintain
Result: Dismissed
References: Article 29, paragraph (2), Article 36, paragraph (4), item (i), and paragraph (6), item (i) of the Patent Act
Related rights, etc.: Patent No. 6353838
Decision of the JPO: Invalidation Trial No. 2021-800003

Summary of the Judgment

1. This is a lawsuit for rescission of a decision by the Japan Patent Office (JPO) that maintained the patent held by the Defendants for an invention titled "Method for treating atopic dermatitis by administering an IL-4R antagonist" (Patent No. 6353838). The issues of the case (grounds for rescission) are: [i] lack of an inventive step; [ii] violation of the support requirement; and [iii] violation of the enablement requirement.
2. In this judgment, the court determined that none of the grounds for rescission argued by the Plaintiff can be found and dismissed the Plaintiff's claim, while holding as summarized below.
(1) Lack of an inventive step (Grounds for Rescission 1)
A. Misunderstanding of common general technical knowledge

The Plaintiff argues that it is inappropriate for the JPO to have determined in its decision (the "JPO Decision"), as common general technical knowledge on atopic dermatitis, that there are an acute phase and a chronic phase, and that in the chronic phase, production of interferon gamma and IL-12 becomes more dominant than that of Th2 cytokines such as IL-4. However, in light of the statements in the relevant document, the "acute phase" and "chronic phase" referred to in the common general technical knowledge on atopic dermatitis as determined in the JPO Decision can be understood as meaning "acute lesion" and "chronic lesion" of rash. It is found that it was common general technical knowledge as of the priority date of the Patent that

atopic dermatitis has a mechanism of action wherein Th2 cells are dominant in the acute phrase when inflammation is strong (acute lesion), whereas Th1 cells become dominant in the chronic state (chronic lesion), and the dominance fluctuates between Th2 cells and Th1 cells (the Th1/Th2 balance changes) depending on the inflamed area and disease stage. Therefore, the determination in the JPO Decision regarding the common general technical knowledge cannot be found to be erroneous.

B. Error in the determination on whether a person ordinarily skilled in the could have easily conceived of the Corrected Invention

It was common general technical knowledge as of the priority date of the Patent that the Th1/Th2 balance changes depending on the inflamed area and disease stage and it was difficult to understand allergic diseases only on the basis of this balance. Even though, before the priority date, specific cells and cytokines (Th2/IL-4) were known as antigens that can be targeted by the compounds (antibodies, etc.) which can be used to treat atopic dermatitis, it was known that many other cells and cytokines also work, and it cannot be said that under such circumstances, a person ordinarily skilled in the art could have even been aware of whether inhibiting the action of Th2/IL-4 would be therapeutically effective on chronic atopic dermatitis, including that suffered by the patients in question (the "Patients").

In addition, the trials in Exhibit Ko 1 are Phase II trials, and in light of the low success rate for the transition from Phase I trials to Phase II trials and the transition from Phrase II trials to Phase III trials, as well as the fact that the information contained in Exhibit 1 is nothing more than a protocol of clinical trials, it cannot be said that a person ordinarily skilled in the art would have understood that the investigational new drug stated in Exhibit Ko 1 is obviously therapeutically effective without looking at the test results.

There is no error in the determination in the JPO Decision that the Corrected Invention could not have been easily made by a person ordinarily skilled in the art.

(2) Violation of the support requirement (Grounds for Rescission 2)

Taking into account the statements in the Description and common general technical knowledge together, it can be said that a person ordinarily skilled in the art who has read the Description would have understood that the therapeutic effect on atopic dermatitis observed when mAb1 is administered to the Patients is produced by the function of mAb1 combining with IL-4R and blocking IL-4, or in other words, its function as an antagonist. It is found that such person could have reasonably recognized that not only mAb1 but also any anti-IL-4R antagonist antibody that combines with IL-4R and blocks IL-4 (the "Antibody, etc.") would have a therapeutic effect on the Patients,

and could have obtained the recognition that the problem targeted by the Corrected Invention can be solved.

(3) Violation of the enablement requirement (Grounds for Rescission 3)

It is found that, based on the statements in the detailed explanation of the invention in the Description and the common general technical knowledge at the time of filing of the application regarding the Patent, a person ordinarily skilled in the art could have reasonably understood that the anti-IL-4R antagonist antibody that combines with IL-4R and blocks IL-4, that is, the antibody based on Corrected Invention 1, can be produced without excessive trial and error, by applying the publicly known method and screening, and that this antibody would have a therapeutic effect when it is administered to the Patients.

Judgment rendered on August 7, 2024
2023 (Gyo-Ke) 10019 Case of seeking rescission of the JPO decision
Date of conclusion of oral argument: June 17, 2024

Judgment

Plaintiff (petitioner in the trial for invalidation)
Kaken Pharmaceutical Co., Ltd.

Defendant (respondent in the trial for invalidation)
Regeneron Pharmaceuticals, Inc.

Defendant (respondent in the trial for invalidation)
Sanofi Biotechnology SAS

Main Text

1. The Plaintiff's claim shall be dismissed.
2. The Plaintiff shall bear the court costs.

Facts and Reasons

(The abbreviations used in the decision made by the Japan Patent Office (JPO) for the present case are also used in this judgment.)

No. 1 Claim

The decision made by the JPO on January 13, 2023, for the case of Invalidation Trial No. 2021-800003 shall be rescinded.

No. 2 Outline of the case

1. Progress of procedures at the JPO, etc. (facts for which there is no dispute between the parties)

(1) On June 15, 2018, the Defendants obtained registration of the establishment of a patent right (Patent No. 6353838; number of claims: 16; the Patent) for a patent application (Patent Application No. 2015-531149), for which the international filing date is September 4, 2013 (with priority claims under the Paris Convention made based on eight applications, including a US patent application filed on September 7, 2012), relating to an invention titled "Methods for treating atopic dermatitis by administering an IL-4R antagonist."

(2) On January 15, 2021, the Plaintiff requested a trial for patent invalidation with regard to the Patent (relating to Claims 1 through 16), and the JPO examined the case

as Invalidation Trial No. 2021-800003.
(3) On April 5, 2022, the Defendants requested a correction to correct the claims of the Patent as described in Attachment "Statement of the Claims of the Patent" (this correction is hereinafter referred to as the "Correction") (the number of claims after the correction: 16).
(4) On January 13, 2023, the JPO approved the Correction, and rendered a decision to the effect that "the request for a trial is groundless" (the JPO Decision). A certified copy of the decision was served on the Plaintiff on January 23, 2023.
(5) On February 21, 2023, the Plaintiff filed the present lawsuit seeking rescission of the JPO Decision.
2. Content of the Corrected Invention
(1) Statement of the Claims

The statement of the claims of the Patent (after the Correction) is as described in Attachment "Statement of the Claims of the Patent," and the statement of Claim 1 is as follows (the underlined part results from the Correction; Claims 2 through 16 are dependent claims of Claim 1; hereinafter, the inventions stated in the respective claims are referred to as "Corrected Invention 1" and the like according to their claim numbers, and are sometimes collectively referred to as the "Corrected Invention").
[Claim 1]

A pharmaceutical composition comprising a therapeutically effective amount of an anti-human interleukin-4 receptor (IL-4R) antibody or antigen-binding fragment thereof to be used in methods to treat moderate-to-severe atopic dermatitis (AD) in patients, which is said pharmaceutical composition where said patients are patients inadequately responsive to treatment with a topical corticosteroid or a topical calcineurin inhibitor or for whom said topical treatment is not recommended.
(Hereinafter, the anti-human interleukin-4 receptor (IL-4R) antibodies are sometimes referred to as the "Antibodies," the Antibodies and the antigen-binding fragments thereof are sometimes collectively referred to as the "Antibodies, etc.," and the target patients stated in Claim 1 are sometimes referred to as the "Patients.")
(2) An extract from the description and drawings of the present case is shown in the Attachment. According to this, the description of the present case (the "Description") is found to disclose the following.
A. Technical field

The present invention relates to the treatment and/or prevention of atopic dermatitis and related conditions. More specifically, the invention relates to the administration of interleukin-4 receptor (IL-4R) antagonists to treat or prevent atopic dermatitis in a

patient in need thereof ([0001]).

B. Background art

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus (e.g., severe itch) and by scaly and dry eczematous lesions. AD is often associated with other atopic disorders such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to major psychological problems, significant sleep loss, and impaired quality of life, leading to high socioeconomic costs ([0002]).

The pathophysiology of AD is influenced by a complex interplay between Immunoglobulin E (IgE)-mediated sensitization, the immune system, and environmental factors. The primary skin defect may be an immunological disturbance that causes IgE-mediated sensitization, with epithelial-barrier dysfunction that is the consequence of both genetic mutations and local inflammation. AD often begins in childhood before age 5 and may persist into adulthood ([0003]).

C. Problem to be solved by the invention

Typical treatments for AD include topical lotions and moisturizers, topical corticosteroid ointments, creams or injections. Most treatment options, however, offer only temporary, incomplete, symptom relief. Moreover, many patients with moderate-to-severe AD become resistant to treatment by topical corticosteroids or by calcineurin inhibitors. Thus, a need exists in the art for novel targeted therapies for the treatment and/or prevention of AD ([0004]).

D. Means for solving the problem

The Corrected Invention relates to methods for treating, preventing and/or reducing the severity of symptoms of atopic dermatitis (AD), including moderate-to-severe AD, and particularly relates to methods for treating, ameliorating or preventing moderate-to-severe AD in a patient who is resistant to treatment by a topical corticosteroid or a calcineurin inhibitor. The methods of the Corrected Invention comprise administering to a subject or a patient in need thereof a pharmaceutical composition comprising a therapeutically effective amount of an interleukin-4 receptor (IL-4R) antagonist, and according to certain embodiments of the Corrected Invention, the IL-4R antagonist is an antibody or antigen-binding fragment thereof that specifically binds IL-4R ([0005]). In addition, the Corrected Invention includes a pharmaceutical composition comprising an anti-IL4R antibody antagonist or an antigen binding fragment thereof for use in the treatment and/or prevention of AD and related conditions ([0027]).

E. Modes for carrying out the invention

An "IL-4R antagonist" is any agent which binds to or interacts with IL-4R and

inhibits the normal biological signaling function of IL-4R when IL-4R is expressed on a cell in vitro or in vivo, and its non-limiting examples include antibodies or antigen-binding fragments of antibodies that specifically bind human IL-4R ([0096]). Anti-IL-4R antibodies that can be used in the Corrected Invention were generated as described in US Patent No. 7,608,693 (Exhibits Ko 3 and 22), as indicated in Example 1. Tables 1 and 2 show 33 types of anti-IL-4R antibodies together with their SEQ ID NOs, and indicate, as one of these types, an anti-IL-4R antibody having the binding characteristics of the reference antibody referred to as "mAb1" (e.g., an antibody or antigen-binding fragment thereof comprising the complementarity determining regions of mAb1), which comprises complementarity determining regions (CDRs) in a heavy chain variable region (HCVR) / light chain variable region (LCVR) sequence pair of SEQ ID NOs: 162/164 (H1H098-b in Table 1) ([0005] and [0153] through [0156]).

In some embodiments, the pharmaceutical composition comprises 75 mg to 600 mg or 300 mg of the anti-IL-4R antibody or antigen-binding fragment thereof ([0034]).

3. Regarding Exhibit Ko 1

Exhibit Ko 1 (Clinical Trials. Gov archive, History of Changes for Study: NCT01548404, Study of REGN668 in Adult Patients With Extrinsic Moderate-to-Severe Atopic Dermatitis), which is the primary cited document for later-mentioned Grounds for Invalidation 1 (lack of an inventive step), is a clinical study protocol (the date of final update and submission: April 19, 2012) that the Defendants, which are the study sponsor and collaborator of "Study of REGN668 in Adult Patients With Extrinsic Moderate-to-Severe Atopic Dermatitis" (the official title: "A Randomized, Double-Blind, Placebo-Controlled, Repeat-Dose Study of the Efficacy, Safety, Tolerability, and Pharmacodynamics of Subcutaneously-Administered REGN668 in Adult Patients With Extrinsic Moderate-to-Severe Atopic Dermatitis"), submitted with regard to the study to the regulatory authority, the U.S. Food and Drug Administration (FDA) (a document output from an information database).

REGN668, which is (a part of) the investigational new drug composition, is an anti-human IL-4R antibody (one of the Antibodies), and it is the same substance as "mAb1" stated in the Description as an example of the Corrected Invention (an undisputed fact).

4. Summary of the JPO Decision

As the question of whether the Correction is appropriate is not disputed in the present lawsuit, a summary of the JPO Decision is given as follows to the extent that is relevant to the grounds for rescission stated in 5. below (if the documentary evidence number differs between the present lawsuit and the trial, the documentary evidence number in the trial is also indicated alongside for reference [documentary evidence

without such indication has the same number in both the present lawsuit and the trial]).
(1) Regarding Grounds for Invalidation 1 (lack of an inventive step based on a cited invention)
A. Exhibit Ko 1 contains the following "cited invention," and the common features and differences between Corrected Invention 1 and the cited invention are as follows.
[Cited invention]

"An investigational new drug composition comprising REGN668 to be used in studies to assess matters such as the effects and safety regarding moderate-to-severe atopic dermatitis (AD) patients, which is said investigational new drug composition where said patients are aged 18 years or older, have had chronic atopic dermatitis for at least 3 years, and are inadequately responsive to treatment with a topical corticosteroid or a topical calcineurin inhibitor."

[Common feature]

The invention is a composition comprising an anti-human IL-4R antibody or antigen-binding fragment thereof, and is administered to patients with moderate-to-severe atopic dermatitis (AD) who are inadequately responsive to treatment with a topical corticosteroid or a topical calcineurin inhibitor.

[Difference]

Corrected Invention 1 is a pharmaceutical composition comprising a therapeutically effective amount of an anti-human interleukin-4 receptor (IL-4R) antibody or antigen-binding fragment thereof to be used in methods to treat patients with moderate-to-severe atopic dermatitis (AD) who are inadequately responsive to treatment with a topical corticosteroid or a topical calcineurin inhibitor, whereas the cited invention is an investigational new drug composition.

B. Common general technical knowledge relating to atopic dermatitis

According to Exhibits Ko 23 through 27 (Trial Exhibits Otsu 3 through 7), it is found to have been common general technical knowledge as of the priority date of the Patent that, in atopic dermatitis, the Th1/Th2 balance changes in a complex manner depending on the disease stage and affected area, and production of Th2 cytokines, such as IL-4 and IL-13, is dominant in the acute phase, whereas in the chronic phase, production of interferon gamma and IL-12 becomes more dominant than that of Th2 cytokines, such as IL-4.

C. Regarding whether a person ordinarily skilled in the art could have easily conceived of the difference

While the study in Exhibit Ko 1 is a Phase 2 clinical trial, it is common general technical knowledge that a Phase 1 clinical trial conducted prior to Phase 2 is intended

for investigating the safety and pharmacokinetics of the investigational new drug in normally a small number of healthy individuals, and that the efficacy of the drug in patients starts to be confirmed from a Phase 2 clinical trial. In addition, according to Exhibit Ko 21 (Trial Exhibit Otsu 1), the probability of success of Phase 2 clinical trials is far lower than that of any other phase, and it is approximately 33% in the case of allergic diseases. In light of this, it cannot immediately be said from the fact that a Phase 2 clinical trial was conducted that a person ordinarily skilled in the art would have understood that the investigational new drug is obviously therapeutically effective without looking at the study results.

Even if Exhibits Ko 2 through 6 are examined, there is no evidence indicating that an anti-human IL-4R antibody was administered to atopic dermatitis patients and therapeutic effects were actually obtained prior to the priority date of the Patent.

Taking into account the common general technical knowledge as of the priority date of the application for the Patent regarding the role of cytokines in the acute phase and chronic phase of atopic dermatitis, even if REGN668 (an anti-human IL-4R antibody) used in Exhibit Ko 1 is able to block IL-4 activity and IL-13 activity, similar to antibodies based on Exhibit Ko 3, it cannot be said that a person ordinarily skilled in the art would have conceived of making a therapeutically effective use of REGN668 (an anti-human IL-4R antibody) in the patients in the cited invention who had had chronic atopic dermatitis for at least 3 years and hence, unlike in the acute phase when production of IL-4 is dominant, production of interferon gamma and IL-12 in those patients was considered to be more dominant than that of IL-4, and a person ordinarily skilled in the art is found to have been unable to easily predict that REGN668 would improve the clinical symptoms.

Moreover, as stated in Exhibit Ko 24 (Trial Exhibit Otsu 4), when considering the complexity of immune pathways that lead to atopic dermatitis, it is found to have been difficult for a person ordinarily skilled in the art to predict that a therapeutic drug based on a specific mechanism, namely, blocking the action of IL-4, which had not been used for treating atopic dermatitis as of the priority date of the Patent, would have therapeutic effects on moderate-to-severe atopic dermatitis, without waiting for the clinical trial results.

Then, it cannot be said that a person ordinarily skilled in the art would have easily determined from the statements in Exhibits Ko 1 through 6 that the cited invention has a structure relating to the difference with Corrected Invention 1, that is, being a pharmaceutical composition comprising a therapeutically effective amount of an anti-human IL-4R antibody to be used in methods to treat patients with moderate-to-severe

atopic dermatitis who are inadequately responsive to treatment with a topical corticosteroid or a topical calcineurin inhibitor, and that the cited invention actually demonstrates an effect of improving the clinical symptoms of atopic dermatitis as indicated in the Description in patients subject to Corrected Invention 1.

D. Summary

As described above, Corrected Invention 1 could not have been easily made by a person ordinarily skilled in the art based on the cited invention and the statements in Exhibits Ko 1 through 6. In addition, as Corrected Inventions 2 through 16 have further limited Corrected Invention 1, and Corrected Invention 1 could not have been easily made by a person ordinarily skilled in the art based on the invention stated in Exhibit Ko 1 and the statements in Exhibits Ko 1 through 6, it is clear that Corrected Inventions 2 through 16 also could not have been easily made by a person ordinarily skilled in the art based on the invention stated in Exhibit Ko 1 and the statements in Exhibits Ko 1 through 6.

(2) Regarding Grounds for Invalidation 2 (violation of the support requirement)

In light of the statement "Typical treatments for AD include topical lotions and moisturizers, topical corticosteroid ointments, creams or injections. Most treatment options, however, offer only temporary, incomplete, symptom relief. Moreover, many patients with moderate-to-severe AD become resistant to treatment by topical corticosteroids or by calcineurin inhibitors. Thus, a need exists in the art for novel targeted therapies for the treatment and/or prevention of AD." in [0004] of the Description and the statement of the claims, the problem targeted by the Corrected Invention is found to be to provide a therapeutically effective pharmaceutical composition to be used in methods for treating moderate-to-severe atopic dermatitis (AD) patients who are inadequately responsive to treatment with a topical corticosteroid or a topical calcineurin inhibitor or for whom said topical treatment is not recommended.

Further, as the patients subject to the study in Example 10 in the Description are moderate-to-severe atopic dermatitis patients who meet inclusion criterion (6) "history of inadequate response to a stable (≥ 1 month) regimen of topical corticosteroids or calcineurin inhibitors as treatment for AD within the last 3 months before the screening visit" ([0354]), it can be said that Example 10 confirms and states that significant improvement was observed in IGA, EASI, BSA, SCORAD, and NRS pruritus, which are indicators for clinically assessing the severity of atopic dermatitis, in a study in which mAb1, an anti-IL-4R, was actually administered to patients subject to the Corrected Invention ([0389]), and Example 12 confirms a decrease in TARC (Exhibits Ko 8 and 10), which is a biomarker of atopic dermatitis that is known to increase in line

with an increase in severity, and a decrease in total IgE (Exhibit Ko 10, [0442]), which is also a biomarker of atopic dermatitis, in the same subject patients, obtaining results consistent with improvement in clinical symptoms.

[0096] of the Description states as follows: "As used herein, an 'IL-4R antagonist' is any agent which binds to or interacts with IL-4R and inhibits the normal biological signaling function of IL-4R when IL-4R is expressed on a cell in vitro or in vivo. Non-limiting examples of categories of IL-4R antagonists include small molecule IL-4R antagonists, …and antibodies or antigen-binding fragments of antibodies that specifically bind human IL-4R." As described in this statement, an anti-human IL-4R antibody in the Corrected Invention is construed to mean an antibody which acts as an IL-4R antagonist that inhibits the normal biological signaling function of IL-4R, and mAb1 also has such action. Further, as it is found to have been common general technical knowledge as of the filing date of the present application that IL-4 promotes production and secretion of IgE (Exhibits Ko 3 and 8), the suppression in the total IgE level in patients who were administered mAb1 in Example 10 is presumed to have been caused by the IL-4 blocking action of mAb1.

Then, it is natural for a person ordinarily skilled in the art to understand from these statements in the Description that the improvement in atopic dermatitis disease symptoms by mAb1 is caused by its blocking of IL-4/IL-13 actions, or in other words, its action as an anti-human IL-4R antibody. Moreover, as described above, an anti-human IL-4R antibody in the Corrected Invention is construed to mean an antibody that acts as an IL-4R antagonist that inhibits the normal biological signaling function of IL-4R according to the statements in [0096]. Therefore, it can be said that antibodies or antigen-binding fragments of antibodies that specifically bind human IL-4R in the Corrected Invention all show an effect to improve atopic dermatitis disease symptoms, in the same way as mAb1.

In light of the above, it is found that a person ordinarily skilled in the art would have been able to obtain an anti-human IL-4R antibody, other than mAb1, that is effective for treating the Patients in the Corrected Invention from the statements in the detailed explanation of the invention, by taking into consideration the common general technical knowledge at the time of filing of the application regarding the Patent.

Due to the above, the patent for the inventions relating to corrected Claims 1 through 16 is not a patent that has been granted for a patent application that fails to meet the requirement prescribed in Article 36, paragraph (6), item (i) of the Patent Act, and therefore, it should not be invalidated based on Grounds for Invalidation 2.

(3) Regarding Grounds for Invalidation 3 (violation of the enablement requirement)

Given that multiple antibodies with different amino acid sequences that can neutralize the biological activity of hIL-4 and hIL-13 had been obtained, as stated in Exhibit Ko 3, by a monoclonal antibody production technique, which was common general technical knowledge at the time of filing of the application regarding the Patent, it is found that a person ordinarily skilled in the art would have been able to obtain an anti-human IL-4R antibody, other than mAb1, that is effective for treating the Patients in the Corrected Invention from the statements in the detailed explanation of the invention, by taking into consideration the common general technical knowledge at the time of filing of the application regarding the Patent. Therefore, it can be said that a person ordinarily skilled in the art who has read the Description would have been able to obtain an anti-human IL-4R antibody, which is an active substance in the Corrected Invention, and manufacture the pharmaceutical composition of the Corrected Invention, by taking common general technical knowledge into consideration.

A person ordinarily skilled in the art would have been able to manufacture and use the pharmaceutical composition of the Corrected Invention from the statements in the detailed explanation of the invention in the Description. Therefore, the statements in the detailed explanation of the invention in the Description describe the Corrected Invention clearly and sufficiently to the extent that enables a person ordinarily skilled in the art to work the invention.

Accordingly, the patent for the inventions relating to corrected Claims 1 through 16 is not a patent that has been granted for a patent application that fails to meet the requirement prescribed in Article 36, paragraph (4), item (i) of the Patent Act, and therefore, it should not be invalidated based on Grounds for Invalidation 3.

5. Grounds for Rescission of the JPO Decision

(1) Grounds for Rescission 1 (an error in the determination on an inventive step; related to Corrected Inventions 1 through 16)

(2) Grounds for Rescission 2 (violation of the support requirement; related to Corrected Inventions 1 through 16)

(3) Grounds for Rescission 3 (violation of the enablement requirement; related to Corrected Inventions 1 through 7 and 10 through 16)

No. 4 Summary of the court decision

1. Regarding Grounds for Rescission 1 (an error in the determination on an inventive step)

(1) Regarding arguments on misunderstanding of common general technical knowledge

A. With regard to the finding in the JPO Decision to the effect that, as common general

technical knowledge on atopic dermatitis, there are an acute phase and a chronic phase, and that in the chronic phase, production of interferon gamma and IL-12 becomes more dominant than that of Th2 cytokines, such as IL-4, the Plaintiff argues that (A) as atopic dermatitis is a chronic disease, the finding runs contrary to common general technical knowledge in that it assumes the presence of an acute phase, and that (B) in atopic dermatitis, Th2 cytokines, such as IL-4, are dominant regardless of the disease stage and the affected area, and the abovementioned finding in the JPO Decision runs contrary to common general technical knowledge.

B. Regarding this point, atopic dermatitis is found to be defined as "a disease in which the main lesion is eczema with pruritus, which repeats remission and relapse" (Exhibits Ko 12 and 28), "one of the representative diseases that involves chronic inflammation" (Exhibit Ko 26), and "a disease included in the eczema/dermatitis group characterized by chronic inflammation and pruritus" (Exhibit Ko 39); therefore, it can be said that atopic dermatitis is a so-called chronic disease. In addition, p. 326 of the Japanese Dermatological Association Guidelines for the Management of Atopic Dermatitis (The Japanese Journal of Dermatology: 118 (3). 325-3422008 [2008]) in Exhibit Ko 39 states, as a diagnostic criterion for atopic dermatitis, that the rash is an eczematous lesion, which is divided into an "acute lesion" (erythema, exudation, papules, vesiculopapules, scales, and crusts) and a "chronic lesion" (infiltrated erythema, lichenification, prurigo, scales, and crusts). These can be said to be in line with the Plaintiff's argument to a certain extent.

C. However, there are statements of documents that conform to the common general technical knowledge determined by the JPO Decision in No. 2, 4. (1) B. above, as described below.

• Exhibits Ko 23 and 48 (*J Allergy Clin Immunol*, March 1996, Vol. 97, No. 3): "In the initiation phase, IL-4 production by T_{H2} and T_{H0} cells is predominant over interferon-γ production by T_{H1} and T_{H0} cells. In the late and chronic phases, the situation is reversed and interferon-γ production by T_{H1} and T_{H0} cells predominates over IL-4 production by T_{H2} and T_{H0} cells."

• Exhibit Ko 24 (*J. Clin. Invest.*, Mar 2004, Vol. 113, No. 5, pp. 651-657): "AD inflammation is associated with increased Th2 cells in acute skin lesions," "acute skin lesions have a significantly greater number of IL-4, IL-5, and IL-13 mRNA–expressing cells," and "chronic AD skin lesions have significantly fewer IL-4 and IL-13 mRNA–expressing cells."

• Exhibit Ko 25 (*Folia Pharmacol. Jpn.*, 2008, Vol. 131, pp. 22-27): "A Th2 cell dominant state observed in the initial phase gradually transitions to a Th1 cell dominant

state."
• Exhibit Ko 26 (*J. Tokyo Med. Univ.*, January 2012, Vol. 70, No. 1, pp. 128-130): "Th2 cells are dominant in the acute phase when inflammation is strong, whereas Th1 cells become dominant in the chronic state, and the dominance fluctuates between Th2 cells and Th1 cells."
• Exhibit Ko 27 (*Jpn. J. Med. Mycol.*, 2004, Vol. 45, No. 3, pp. 137-142): "It is thought that Th2 cytokines, such as IL-4 and IL-5, cause inflammation in the acute phase of atopic dermatitis, whereas in the chronic phase, Th1 cells that produce IFNγ are responsible for amplifying inflammation."
• Exhibit Otsu 21 (a medical paper titled "Control of inflammation in atopic dermatitis," Vol. 20, No. 5, September 2000): "in the initial phase … Th2 cytokines probably play the main role, and not only Th2 cytokines, but also Th1 cytokines are considered to be involved in maintaining inflammation" (p. 584).
D. In light of these statements, it was indicated that Th2 cells that produce the cytokines referred to as IL-4 or IL-13 increase at the focal area (acute lesion) in the acute phase of atopic dermatitis, whereas Th1 cells that produce IFN-γ increase at the inflamed area (chronic lesion) in the chronic phase. Thus, it is found that it was common general technical knowledge as of the priority date of the Patent that atopic dermatitis has a mechanism of action where Th2 cells are dominant in the acute phase when inflammation is strong (acute lesion), whereas Th1 cells become dominant in the chronic state (chronic lesion), and the dominance fluctuates between Th2 cells and Th1 cells (the Th1/Th2 balance changes) depending on the inflamed area and disease stage.

Meanwhile, there are documents indicating a strong involvement of a Th2 cytokine called IL-13 in atopic dermatitis (Exhibit Ko 76, etc.) as argued by the Plaintiff. Even so, however, it cannot be said that there was an error in the determination in the JPO Decision regarding common general technical knowledge to the effect that it was "common general technical knowledge as of the priority date of the Patent that, … in the chronic phase, production of interferon gamma and IL-12 becomes more dominant than that of Th2 cytokines, such as IL-4."
E. While the Plaintiff's argument denies the concept of an acute phase and a chronic phase itself regarding atopic dermatitis, the basis for this argument is understood to be that atopic dermatitis is a chronic disease, and it is only that the lesion of rash is divided into an "acute lesion" and a "chronic lesion" (see B. above). However, in light of the statements in the documents found in C. above, the "acute phase" and "chronic phase" referred to in the common general technical knowledge on atopic dermatitis as determined in No. 2, 4. (1) B. above in the JPO Decision can be understood as meaning

"acute lesion" and "chronic lesion" of rash, and even by taking into account the points argued by the Plaintiff, the determination regarding the common general technical knowledge cannot be found to be erroneous.

F. According to the above, none of the Plaintiff's arguments pointing out the misunderstanding of common general technical knowledge in the JPO Decision can be accepted. In addition, while the Plaintiff has made various arguments, such as the misunderstanding of the effects of the cited invention, based on the premise of that misunderstanding of common general technical knowledge, none of these arguments can be accepted due to lack of the premise.

(2) Error in the determination on whether a person ordinarily skilled in the could have easily conceived of the Corrected Invention

A. The Plaintiff argues that a Phase I trial of REGN668 was conducted on atopic dermatitis patients prior to the study in Exhibit Ko 1 (Phase II trial), and that it was already determined that REGN668 relating to the cited invention is a drug that is expected to have utility as a pharmaceutical product, and thus a person ordinarily skilled in the art could have predicted that REGN668, an anti-human IL-4 antibody, would be effective, in light of the correct common general technical knowledge that atopic dermatitis is a disease in which Th2/IL-4, etc. are dominant.

B. However, the common general technical knowledge on atopic dermatitis as determined in the JPO Decision, that is, atopic dermatitis has a mechanism of action where Th2 cells are dominant in the acute phase when inflammation is strong (acute lesion), whereas Th1 cells become dominant in the chronic state (chronic lesion), and the dominance fluctuates between Th2 cells and Th1 cells (the Th1/Th2 balance changes) depending on the inflamed area and disease stage, contains no error as discussed in (1) above, and the efficacy of the drug in treatment cannot be determined merely based on a simple understanding that "atopic dermatitis is a disease in which Th2/IL-4, etc. are dominant" as argued by the Plaintiff.

Moreover, the fact that immune pathways of atopic dermatitis are complex and could change depending on the inflamed area and disease stage is as indicated in the following: the statement "Insights into the role that certain cells and cytokines play in AD create opportunities for the development of targeted therapy. However, given the complexity of the biological processes involved, none of the tested compounds to date has proven to be the magic bullet." in Exhibit Ko 24 mentioned above; the statement "as the Th1/Th2 balance may change even at a relatively limited site and depending on the disease stage, and further, as the balance may differ depending on the sites within the same individual, it is considered to be unreasonable to understand allergic diseases

based on the Th1/Th2 balance alone" in Exhibit Ko 25 mentioned above; the statement "various cells and chemical messengers produced or released by them, cytokines, chemokines, etc. are comprehensively involved in the inflammation of atopic dermatitis" in Exhibit Ko 28 (a PDF material titled "Atopic Dermatitis" on the website of the Ministry of Health, Labour and Welfare); and the statements "it is presumed that in the initial phase of AD, the rash is completed with Th2 cytokines playing the main role, after which Th1 cytokines are also expressed, and both cytokines are intricately involved in maintaining the dermatitis" and "as mentioned above, in inflammation (dermatitis) that has already occurred, not only Th2 cytokines, but also Th1 cytokines, and various other kinds of immune cells are intricately involved" in Exhibit Otsu 21 mentioned above.

When also considering such complexity of immune pathways that lead to atopic dermatitis, it was common general technical knowledge as of the priority date of the Patent that the Th1/Th2 balance changes depending on the inflamed area and disease stage and it is difficult to understand allergic diseases only on the basis of this balance. Before that, it can be said that the understanding by a person ordinarily skilled in the art about the role that certain cells and cytokines, including IL-4 and Th2 cells that produce IL-4, play in atopic dermatitis was limited to the creation of opportunities for the development of targeted therapy (making it possible to search for candidate compounds by targeting certain cells and cytokines), and did not reach the level of elucidating the existence of a compound (an antibody, etc.) that enables treatment of atopic dermatitis by targeting any of the certain cells and cytokines.

Then, even though, before the priority date, certain cells and cytokines (Th2/IL-4) were known as antigens that can be targeted by the compounds (antibodies, etc.) which can be used to treat atopic dermatitis, it was known that many other cells and cytokines also work, and it cannot be said that under such circumstances, a person ordinarily skilled in the art could have even been aware of whether inhibiting the action of Th2/IL-4 would be therapeutically effective on chronic atopic dermatitis, including that suffered by the Patients. In other words, even if an antibody (anti-IL-4R antibody) against a receptor that inhibits the action of such antigen was publicly known, there was no publicly known information that a drug trial demonstrated that inhibition of such action has therapeutic effects on atopic dermatitis, and therefore, it can be said that whether that antibody (anti-IL-4R antibody) has therapeutic effects on atopic dermatitis could not be predicted unless it was actually used in a drug trial and its effects on atopic dermatitis were confirmed.

C. In addition, the study in Exhibit Ko 1 is a Phase II trial, and according to Exhibit Ko

21, it is found that the success rate for the transition from Phase I trials (Phase 1) is 63.2% (n = 3,582), and the success rate for the transition from Phase II trials to Phase III trials is even lower at merely 30.7% (n = 3,862; 33% for allergic diseases). Further, the information contained in Exhibit Ko 1 is nothing more than a protocol of a clinical trial, and it does not contain the actual study results. Thus, it cannot be said that a person ordinarily skilled in the art would have understood that the investigational new drug stated in Exhibit Ko 1 is obviously therapeutically effective without looking at the study results.

D. In response, the Plaintiff argues that, with regard to the "therapeutically effective amount" relating to the difference between Corrected Invention 1 and the cited invention, the amount of the investigational new drug to be studied in a clinical trial for confirming the drug efficacy (Exhibit Ko 1) is obviously a therapeutically effective amount, and that the specific doses of human antibodies against atopic dermatitis are stated in Exhibit Ko 3, which was publicly known at the time of making the cited invention.

However, even by taking into account the abovementioned argument, as the inhibition of the action of Th2/IL-4 itself was not established knowledge, it does not affect the abovementioned determination that it cannot be said that a person ordinarily skilled in the art could have been aware of whether inhibiting the action of Th2/IL-4 would be therapeutically effective on chronic atopic dermatitis, including that suffered by the Patients. Further, the statement "normally at a single dose of about 0.01 to about 20 mg/kg body weight" in Exhibit Ko 3 is a dose guideline for cases in which the antibody is used for treating various conditions and diseases associated with IL-4, and no information is indicated on the dose for the Patients subject to the Corrected Invention.

Accordingly, the Plaintiff's abovementioned argument cannot be accepted.

E. In addition, the Plaintiff argues that the structure of being "pharmaceutical" is not a substantial difference, asserting that, while Exhibit Ko 1 indicates REGN668 as an investigational new drug, an investigational new drug and a pharmaceutical composition are no different, and that it is obvious that utility can be expected in an investigational new drug composition that has undergone Phase I trial and has been put to a Phase II trial, which is a further clinical trial. The Plaintiff also argues that there is a statement in Exhibit Ko 2 which refers to REGN668 as "medications."

However, Exhibit Ko 1 has no statements indicating that REGN668 is therapeutically effective on the Patients and can be put to a pharmaceutical use. In addition, Exhibit Ko 2 also only states that "two medications that are currently in AD

clinical trials are directed against IL-4 receptor (Aeroderm and REGN-668)," in which the term "medications" is understood to have been used in the context that clinical trials on atopic dermatitis are being conducted for two medications including "REGN-668," and therefore, it cannot be said that Exhibit Ko 2 states that REGN668 can be put to a pharmaceutical use.

Accordingly, the Plaintiff's abovementioned argument on the structure of being "pharmaceutical" also cannot be accepted.

F. Apart from the above, the Plaintiff also argues that the only example in the Description that fulfills the entire structure of the Corrected Invention is the mAb1 antibody in Examples 8 and 10, and that the Description does not disclose other antibodies and antigen-binding fragments of antibodies. However, as this point should be examined in relation to the support requirement, it will be discussed in 2. below.

(3) Summary

According to the above, none of the Plaintiff's arguments regarding Grounds for Rescission 1 can be accepted, and no error is found in the determination in the JPO Decision that Corrected Invention 1 could not have been easily made by a person ordinarily skilled in the art based on the cited invention and the statements in Exhibits Ko 1 through 6.

In addition, as Corrected Inventions 2 through 16 have further limited Corrected Invention 1, there is also no error in the determination in the JPO Decision that Corrected Inventions 2 through 16 could not have been easily made by a person ordinarily skilled in the art.

2. Regarding Grounds for Rescission 2 (violation of the support requirement)

(1) The Plaintiff argues that the JPO Decision is erroneous in regard to compliance with the support requirement, stating that, while the pharmacological study results disclosed in the Description relate to mAb1, the Corrected Invention comprises antibodies, etc. that differ from mAb1 in terms of binding affinity and pharmacokinetics, and a person ordinarily skilled in the art would not recognize that it can be used in clinical treatment, and that as a result, the scope of right of the Patent has become significantly broader than in the disclosure in the Description.

Regarding this point, Article 36, paragraph (6), item (i) of the Patent Act provides for the support requirement, which requires the invention stated in the claims to be substantially supported by the detailed explanation of the invention. It is construed that whether the statement of the claims satisfies the support requirement should be determined by considering, through comparison of the statement of the claims and the statement of the detailed explanation of the invention, whether the invention described

in the claims is the invention described in the detailed explanation of the invention that is within the scope for which a person ordinarily skilled in the art can recognize, based on the statement of the detailed explanation of the invention, that the invention can solve the problem targeted by the invention, and also by considering whether the invention described in the claims is an invention within the scope for which a person ordinarily skilled in the art can recognize that the invention can solve the problem targeted by the invention, in light of the common general technical knowledge as of the time of filing the application, even without the statement and indication thereof. Accordingly, examination will be made below from this viewpoint.

(2) The problem targeted by the Corrected Invention and the means for solving the problem indicated in the Description are as follows.

A. First, as mentioned in No. 2, 2. (2) above, the Description states the following: atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus (e.g., severe itch) and by scaly and dry eczematous lesions; the pathophysiology of AD is influenced by a complex interplay between Immunoglobulin E (IgE)-mediated sensitization, the immune system, and environmental factors; and the primary skin defect is an immunological disturbance that causes IgE-mediated sensitization, with epithelial-barrier dysfunction that is the consequence of both genetic mutations and local inflammation; meanwhile, typical conventional treatments for AD include topical lotions and moisturizers, topical corticosteroid ointments, creams or injections, but there are problems in that they offer only temporary, incomplete, symptom relief, and moreover, many patients with moderate-to-severe AD become resistant to treatment by topical corticosteroids or by calcineurin inhibitors; thus, a need exists in the art for novel targeted therapies for the treatment and/or prevention of AD.

In light of the above statements and the statement of the claims, the problem targeted by the Corrected Invention is found to be "to provide a therapeutically effective pharmaceutical composition to be used in methods for treating moderate-to-severe atopic dermatitis (AD) patients who are inadequately responsive to treatment with a topical corticosteroid or a topical calcineurin inhibitor or for whom said topical treatment is not recommended."

B. The means for solving the problem is the administration of "a pharmaceutical composition comprising a therapeutically effective amount of an interleukin-4 receptor (IL-4R) antagonist" to patients (No. 2, 2. (2) D. above). The Description states that "interleukin-4 receptor (IL-4R) antagonist" in this context is any agent which binds to or interacts with IL-4R and inhibits the normal biological signaling function of IL-4R when IL-4R is expressed on a cell in vitro or in vivo, and cites antibodies or antigen-

binding fragments of antibodies that specifically bind human IL-4R as its non-limiting examples.

(3) As the basis that supports the solution above, the Description is found to disclose the following.

A. While the antibodies obtained in the examples in the Description were all generated as stated in Exhibit Ko 3 ([0153]), Exhibit Ko 3 is found to disclose a method to obtain an antibody capable of blocking hIL-4 activity and hIL-13 activity, that is, an anti-IL-4R antagonist antibody, by screening anti-IL-4R antibodies obtained by publicly known methods in terms of binding affinity and potency in blocking hIL-4's binding to hIL-4R.

Then, the antibodies based on the Corrected Invention are all found to be anti-IL-4R antagonist antibodies that bind IL-4R and block IL-4 signals.

Example 1 in the Description discloses that 33 types of anti-IL-4R antagonist antibodies, including "mAb1," are generated as stated in Exhibit Ko 3.

B. In addition, Example 8 and Example 10 confirm that significant improvement was observed in IGA, EASI, BSA, SCORAD, and NRS pruritus, which are indicators for assessing the proportion of the lesions, severity, and pruritus of atopic dermatitis in a study in which mAb1 was administered to the Patients ([0324], [0325], and [0389]).

C. Further, "B. Administration of mAb1 to Subjects with Atopic Dermatitis" ([0420]) in Example 12 confirms that, with regard to samples from two separate clinical trials (note: there is the statement "see Example 7 herein," but this is construed to be a typo of Example 8 in light of the contents of the study), decreases in TARC and total IgE were observed as a result of administration of mAb1, and a correlation was found between pruritus (5D score) and CCL17(TARC) levels. In the same way, "C. Repeated Administration of mAb1 to Subjects with Moderate-to-Severe Atopic Dermatitis" ([0440]) in Example 12 confirms, with regard to samples obtained from the target patients who participated in the study in Example 10 (the "Patients"), decreases in TARC and total IgE, which are AD-associated biomarkers that are found to correlate with AD severity and may be involved in the pathogenesis of the disease, obtaining results consistent with improvement in clinical symptoms.

(4) Next, looking at the common general technical knowledge at the time of filing of the application regarding the Patent, which should be taken into account in determining compliance with the support requirement, Exhibit Ko 3 (Column 1, lines 16 to 25) and Exhibit Ko 22 ([0001]) state that "IL-4 induces the expression of class II major histocompatibility complex molecules in resting B cells, and enhances the secretion of IgE and IgG1 isotypes by stimulated B cells." From this, it can be read that IL-4

stimulates resting B cells, and enhances the secretion of IgE. In addition, Exhibit Ko 8 (from S105, right column, line 2 from the bottom to S106, left column, line 7) and Exhibit Ko 32 state that "IL-4 and IL-13 play overlapping roles in allergic diseases, such as inducing the IgE isotype switch." From this, it can be read that if the IgE isotype switch is induced, the secretion of IgE is promoted, and therefore, IL-4 promotes the secretion of IgE. According to the above, it can be said that the production and secretion of IgE is promoted by IL-4.

Moreover, from Exhibit Ko 8 (S106, left column, lines 24 to 25) and paragraphs [0436] and [0441] of the Description, it is found that the fact that TARC is a chemokine induced by IL-4 and IL-13, shown to be strongly associated with disease severity of AD, was common general technical knowledge at the time of filing of the application regarding the Patent.

(5) Taking into account the abovementioned statements in the Description and common general technical knowledge together, as the Description discloses [i] that mAb1 is an anti-IL-4R antagonist antibody that binds IL-4R and blocks IL-4 signals, [ii] that clinical symptoms of atopic dermatitis improved in the Patients administered with mAb1, and [iii] that the levels of TARC and IgE, which are AD-associated biomarkers and whose production and secretion are known to be induced by IL-4, decreased in the Patients administered with mAb1, it can be said that a person ordinarily skilled in the art who has read the Description would have understood that the therapeutic effect on atopic dermatitis observed when mAb1 is administered to the Patients is produced by the action of mAb1 binding IL-4R and blocking IL-4, or in other words, its action as an antagonist.

Then, it is found that such person could have reasonably recognized that not only mAb1 but also any anti-IL-4R antagonist antibodies that bind IL-4R and block IL-4 (the "Antibodies, etc.") would have a therapeutic effect on the Patients, and could have obtained the recognition that the problem targeted by the Corrected Invention mentioned in (2) above can be solved.

(6) Meanwhile, the fact that the pharmacological study results disclosed in the Description only relate to mAb1 is as indicated by the Plaintiff. However, the scope of the support by examples, etc. that would be regarded as being sufficient when determining "whether the invention described in the claims is the invention described in the detailed explanation of the invention that is within the scope for which a person ordinarily skilled in the art can recognize, based on the statement of the detailed explanation of the invention, that the invention can solve the problem targeted by the invention" and other matters with regard to compliance with the support requirement,

should be examined by taking into account the logic through which recognition of the solution to the problem would be derived, and such simple argument as that the number of examples is too small compared to the patent claims is not appropriate.

When this point is examined for the present case, the facts [i] that mAb1 is an anti-IL-4R antagonist antibody that binds IL-4R and blocks IL-4 signals, [ii] that clinical symptoms of atopic dermatitis improved in the Patients administered with mAb1, and [iii] that the levels of TARC and IgE, which are AD-associated biomarkers and whose production and secretion are known to be induced by IL-4, decreased in the Patients administered with mAb1 are disclosed in this case; as a deductively derived inference, it is understood that the therapeutic effect on atopic dermatitis observed when mAb1 is administered to the Patients was produced by the action of mAb1 binding L-4R and blocking IL-4, or in other words, its action as an antagonist. This case differs from a case where the scope for which a person ordinarily skilled in the art can recognize that the invention can solve the problem targeted by the invention is derived inductively from a wide range of examples. The abovementioned mechanism of action is that mAb1, one of the antibodies, binds IL-4R and blocks IL-4 signals, and in the Patients administered with mAb1, clinical symptoms of atopic dermatitis improved and the levels of AD-associated biomarkers also decreased. Therefore, it is clear that a person ordinarily skilled in the art would be able to understand that the Antibodies, etc. which are anti-IL-4R antagonist antibodies other than mAb1 (the 32 types other than mAb1) also have the same action and effect.

The Plaintiff's argument that the pharmacological study results disclosed in the Description only relate to mAb1 does not affect the abovementioned determination.

(7) In addition, the Plaintiff mentions that the Antibodies, etc. include those with completely different binding affinity, blood half-life, preservation stability, etc. as the grounds for violation of the support requirement. However, although there may be a need to screen the Antibodies, etc. that have effects that are needed for treating atopic dermatitis (this point will be discussed later as an issue relating to the enablement requirement), there is no sufficient evidence to find that the differences in binding affinity, blood half-life, preservation stability, etc. deny the abovementioned mechanism of action. Therefore, even if differences in terms of binding affinity, etc. exist among the Antibodies, etc., it cannot be said that they lead to violation of the support requirement, in light of the holding in (6) above.

(8) Summary

According to the above, the Plaintiff's arguments regarding Grounds for Rescission 2 cannot be accepted, and violation of the support requirement as alleged by the Plaintiff

cannot be found.

3. Regarding Grounds for Rescission 3 (violation of the enablement requirement)

(1) The Plaintiff argues that Corrected Inventions 1 through 7 and 10 through 16 violate the enablement requirement because [i] some of the antibodies, etc. stated in the claims of the Patent cannot be used in treatment due to their weak binding affinity, and there is a need to screen those that can be used in clinical treatment, and [ii] the therapeutically effective amount also needs to be confirmed by a clinical trial each time, both of which require excessive trial and error.

Regarding this point, in terms of the enablement requirement provided in Article 36, paragraph (4), item (i) of the Patent Act, it should be examined whether the detailed explanation of the invention in the Description is described clearly and sufficiently to the extent that a person ordinarily skilled in the art can work the invention stated in the claims without excessive trial and error, based on the statements of the detailed explanation of the invention and the common general technical knowledge at the time of filing of the application regarding the Patent.

(2) Based on the framework above, examination is first made on the Plaintiff's argument [i]. As mentioned above, the Antibodies, etc. mean anti-IL-4R antagonist antibodies and antigen-binding fragments thereof, and Example 1 in the Description states that 33 types of anti-IL-4R antagonist antibodies, including "mAb1," were obtained, as stated in Exhibit Ko 3. Meanwhile, Exhibit Ko 3 is found to disclose a method to obtain an antibody capable of blocking hIL-4 activity and hIL-13 activity, that is, an anti-IL-4R antagonist antibody, by screening anti-IL-4R antibodies obtained by methods that were publicly known at the time of filing of the application regarding the Patent in terms of binding affinity and potency in blocking hIL-4's binding to hIL-4R. In addition, according to the statements in examples, it can be understood that, if mAb1 is administered to the Patients, mAb1 will produce a therapeutic effect on atopic dermatitis by the action of mAb1 binding IL-4R and blocking IL-4, or in other words, its action as an antagonist.

Thus, it is found that, based on the statements in the detailed explanation of the invention in the Description and the common general technical knowledge at the time of filing of the application regarding the Patent, a person ordinarily skilled in the art could have reasonably understood that the anti-IL-4R antagonist antibody that binds IL-4R and blocks IL-4, that is, the antibody based on Corrected Invention 1, can be produced without excessive trial and error, by applying the publicly known method and screening, and that this antibody would have a therapeutic effect when it is administered to the Patients.

Accordingly, it can be said that the detailed explanation of the invention in the Description is described clearly and sufficiently to the extent that a person ordinarily skilled in the art can work Corrected Invention 1 without excessive trial and error, based on the statements of the detailed explanation of the invention and the common general technical knowledge at the time of filing of the application regarding the Patent.

(3) Next, when the Plaintiff's argument [ii] (the point that the therapeutically effective amount needs to be confirmed each time) is examined, the Description discloses 300 mg as a specific dose of mAb1 (Example 10) ([0353]), and paragraph [0019], etc. also state guidelines for the dose. Therefore, it cannot go so far as to find that a person ordinarily skilled in the art would require excessive trial and error in setting therapeutically effective amounts also for antibodies other than mAb1 according to the extent of the antagonist activity.

(4) In addition, Corrected Inventions 2 through 7 and 10 through 16 directly or indirectly cite Corrected Invention 1. Therefore, in the same manner as in the examination regarding Corrected Invention 1 in (2) above, it can be said that a person ordinarily skilled in the art can work the invention stated in the claims without excessive trial and error, based on the statements in the Description and the common general technical knowledge at the time of filing of the application regarding the Patent.

(5) Due to the above, the Plaintiff's arguments to the effect that Corrected Inventions 1 through 7 and 10 through 16 violate the enablement requirement cannot be accepted.

4. Conclusion

As discussed above, all of the Plaintiff's arguments regarding the grounds for rescission are groundless, and no illegality is found that would require the JPO Decision to be rescinded. Accordingly, the Plaintiff's claims are dismissed, and the judgment is rendered as indicated in the main text.

Intellectual Property High Court, Fourth Division
Presiding judge: MIYASAKA Masatoshi
Judge: MOTOYOSHI Hiroyuki
Judge: IWAI Naoyuki

Attachment

Statement of the Claims of the Patent

[Claim 1]

A pharmaceutical composition comprising a therapeutically effective amount of an anti-human interleukin-4 receptor (IL-4R) antibody or antigen-binding fragment thereof to be used in methods to treat moderate-to-severe atopic dermatitis (AD) in patients, which is said pharmaceutical composition where said patients are patients inadequately responsive to treatment with a topical corticosteroid or a topical calcineurin inhibitor or for whom said topical treatment is not recommended.

[Claim 2]

A pharmaceutical composition according to Claim 1, where patients have a history of inadequate response to outpatient treatment with a topical corticosteroid or a topical calcineurin inhibitor, and fulfill either or both of the following conditions: [i] fail to achieve an Investigator's Global Assessment (IGA) score of 0 (clear) to 2 (mild) despite being treated with daily application of a topical corticosteroid of moderate-to-high-strength for at least 28 days; or [ii] fail to achieve an IGA score of 0 to 2 despite being treated with daily application of a topical corticosteroid of very high strength for at least 14 days.

[Claim 3]

A pharmaceutical composition according to Claim 1 or 2, where each dose of the pharmaceutical composition administered by said methods comprises 75 mg to 600 mg of an anti-human IL-4R antibody or antigen-binding fragment thereof.

[Claim 4]

A pharmaceutical composition according to any of Claims 1 through 3, where each dose of the pharmaceutical composition administered by said methods comprises 300 mg of an anti-human IL-4R antibody or antigen-binding fragment thereof.

[Claim 5]

A pharmaceutical composition according to Claim 1 or 2, where said methods comprise the administration of the initial dose of a pharmaceutical composition to a patient and the subsequent administration of one or more doses of said pharmaceutical composition to the patient, and each of the subsequent doses is administered to the patient one week or two weeks after the administration of the immediately preceding dose.

[Claim 6]

A pharmaceutical composition according to Claim 5, where the initial dose includes 600 mg of an anti-human IL-4R antibody or antigen-binding fragment thereof and the subsequent doses each include 75 mg to 300 mg of an anti-human IL-4R antibody or antigen-binding fragment thereof.

[Claim 7]

A pharmaceutical composition according to Claim 5, where the initial dosage is two times the subsequent dose.

[Claim 8]

A pharmaceutical composition according to any of Claims 1 through 7, where an antibody or antigen-binding fragment thereof comprises heavy and light complementarity determining regions (CDRs) in a heavy chain variable region (HCVR) / light chain variable region (LCVR), which is an amino acid pair consisting of SEQ ID NOs: 162/164.

[Claim 9]

A pharmaceutical composition according to Claim 8, where an antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining region (HCDR) sequences comprising SEQ ID NOs: 148, 150, and 152, respectively, and three light chain complementarity determining (LCDR) sequences comprising SEQ ID NOs: 156, 158, and 160, respectively.

[Claim 10]

A pharmaceutical composition according to any of Claims 1 through 9, where, after the administration of the pharmaceutical composition, the patient shows an improvement in one or more AD-associated parameters described below, and said improvement in one or more AD-associated parameters is any of the following:

(I) a decrease from baseline in Investigator's Global Assessment (IGA) score of at least 25%;

(II) a decrease from baseline in Pruritus Numeric Rating Scale (NRS) score of at least 25%;

(III) a decrease from baseline in Eczema Area and Severity Index (EASI) score of at least 45%;

(IV) a decrease from baseline in SCORAD score of at least 30%;

(V) a decrease from baseline in 5-D Pruritus Scale of at least 15%; or

(VI) a decrease from baseline in body surface area involvement of atopic dermatitis (BSA) score of at least 35%.

[Claim 11]

A pharmaceutical composition according to Claim 10, where the improvement in

one or more AD-associated parameters is any of the following:
(a) a decrease from baseline in IGA score of at least 35% by day 22 after administration of the first dose of the pharmaceutical composition comprising an anti-human interleukin-4 receptor (IL-4R) antibody or antigen-binding fragment thereof;
(b) a decrease from baseline in NRS score of at least 25% by the end of week 2 after administration of the first dose of the pharmaceutical composition comprising an anti-human interleukin-4 receptor (IL-4R) antibody or antigen-binding fragment thereof;
(c) a decrease from baseline in EASI score of at least 50% by day 29 after administration of the first dose of the pharmaceutical composition comprising an anti-human interleukin-4 receptor (IL-4R) antibody or antigen-binding fragment thereof;
(d) a decrease from baseline in SCORAD score of at least 35% by day 29 after administration of the first dose of the pharmaceutical composition comprising an anti-human interleukin-4 receptor (IL-4R) antibody or antigen-binding fragment thereof; or
(e) a decrease from baseline in 5-D Pruritus Scale of at least 25% or at least 30% by day 85 after administration of the first dose of the pharmaceutical composition comprising an anti-human interleukin-4 receptor (IL-4R) antibody or antigen-binding fragment thereof.

[Claim 12]

A pharmaceutical composition according to Claim 10, where the improvement in one or more AD-associated parameters is a decrease from baseline in BSA score of at least 35% by day 29 after administration of the first dose of the pharmaceutical composition.

[Claim 13]

A pharmaceutical composition according to any of Claims 1 through 12, where the methods specified in Claim 1 further comprise simultaneous administration of a topical corticosteroid.

[Claim 14]

A pharmaceutical composition according to Claim 13, where said method comprises an initial treatment period for administering an anti-human IL-4R antibody or antigen-binding fragment thereof and a topical corticosteroid and a subsequently following period for gradually decreasing the dose of the topical corticosteroid while continuing the administration of the anti-human IL-4R antibody or antigen-binding fragment thereof.

[Claim 15]

A pharmaceutical composition according to Claim 14, where the amount of the topical corticosteroid is decreased by 10%, 20%, 30%, 40%, or 50% or more compared

to the dose during the initial treatment period.

[Claim 16]

A pharmaceutical composition according to any of Claims 1 through 15, where the pharmaceutical composition is administered by subcutaneous injection.

End

Attachment

Statement, etc. of the Description (Extract)

[Technical Field]

[0001]

The present invention relates to the treatment and/or prevention of atopic dermatitis and related conditions. More specifically, the invention relates to the administration of interleukin-4 receptor (IL-4R) antagonists to treat or prevent atopic dermatitis in a patient in need thereof.

[Background Art]

[0002]

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus (e.g., severe itch) and by scaly and dry eczematous lesions. AD is often associated with other atopic disorders such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to major psychological problems, significant sleep loss, and impaired quality of life, leading to high socioeconomic costs.

[0003]

The pathophysiology of AD is influenced by a complex interplay between Immunoglobulin E (IgE)-mediated sensitization, the immune system, and environmental factors. The primary skin defect may be an immunological disturbance that causes IgE-mediated sensitization, with epithelial-barrier dysfunction that is the consequence of both genetic mutations and local inflammation. AD often begins in childhood before age 5 and may persist into adulthood.

[Problem to Be Solved by the Invention]

[0004]

Typical treatments for AD include topical lotions and moisturizers, topical corticosteroid ointments, creams or injections. Most treatment options, however, offer only temporary, incomplete, symptom relief. Moreover, many patients with moderate-to-severe AD become resistant to treatment by topical corticosteroids or by calcineurin inhibitors. Thus, a need exists in the art for novel targeted therapies for the treatment and/or prevention of AD.

[Means for Solving the Problem]

[0005]

According to certain aspects of the present invention, methods are provided for treating, preventing and/or reducing the severity of symptoms of atopic dermatitis (AD), including moderate-to-severe AD. Certain embodiments of the invention pertain to

methods for treating, ameliorating or preventing moderate-to-severe AD in a patient who is resistant to treatment by a topical corticosteroid or a calcineurin inhibitor. In some embodiments, the present invention discloses methods of treating patients with moderate-to-severe AD that is uncontrolled despite treatment with a topical corticosteroid or a calcineurin inhibitor. The methods of the present invention comprise administering to a subject or a patient in need thereof a pharmaceutical composition comprising a therapeutically effective amount of an interleukin-4 receptor (IL-4R) antagonist. According to certain embodiments of the present invention, the IL-4R antagonist is an antibody or antigen-binding fragment thereof that specifically binds IL-4R. Exemplary anti-IL-4R antibodies that can be used in the context of the methods of the present invention are described elsewhere herein, including working Example 1. In certain embodiments, the IL-4R antagonist is an anti-IL-4R antibody having the binding characteristics of the reference antibody referred to herein as "mAb1" (e.g., an antibody or antigen-binding fragment thereof comprising the complementarity determining regions of mAb1). In one embodiment, the antibody or antigen-binding fragment thereof that binds IL-4R comprises complementarity determining regions (CDRs) in a heavy chain variable region (HCVR) / light chain variable region (LCVR) sequence pair of SEQ ID NOs: 162/164.

[0006]

Some embodiments of the invention are directed to methods for treating, reducing, ameliorating or preventing pruritus in a patient, comprising administration of a pharmaceutical composition comprising a therapeutically effective amount of an IL-4R antagonist. In one embodiment, the patient suffers from moderate-to-severe AD. In some embodiments, the patient suffering from AD is resistant to treatment by either a topical corticosteroid or a calcineurin inhibitor.

[0007]

In certain embodiments, the present invention includes methods to treat moderate-to-severe AD in a patient, the methods comprising administering a pharmaceutical composition comprising a therapeutically effective amount of an antibody or antigen-binding fragment thereof that binds IL-4R, and determining an improvement in an AD-associated parameter. The improvement can be determined or assayed or quantitated by methods well-known in the art. AD-associated parameters and improvements therein are discussed elsewhere herein, including e.g., in working Example 7.

[0018]

In certain embodiments, the IL-4R antagonist of the present methods is an antibody or antigen-binding fragment that specifically binds IL-4R and that comprises heavy and

light chain CDR sequences from a HCVR/LCVR sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/20, 22/24, 26/34, 42/44, 46/48, 50/58, 66/68, 70/72, 74/82, 90/92, 94/96, 98/106, 114/116, 118/120, 122/130, 138/140, 142/144, 146/154, 162/164, 166/168, 170/178, 186/188, 190/192, 194/202, 210/212, 214/216, 218/226, 234/236, 238/240, 242/250, 258/260 and 262/264. In one embodiment, the antibody or antigen-binding fragment that specifically binds IL-4R comprises heavy and light chain CDR sequences from the HCVR/LCVR sequence pair of SEQ ID NOs: 162/164. In one embodiment, the antibody or antigen-binding fragment that specifically binds IL-4R comprises three heavy chain complementarity determining region (HCDR) sequences comprising SEQ ID NOs: 148, 150, 152, respectively, and three light chain complementarity determining (LCDR) sequences comprising SEQ ID NOs: 156, 158 and 160, respectively.

[0019]

In some embodiments, the pharmaceutical composition is administered subcutaneously or intravenously to the patient. In some embodiments, the pharmaceutical composition comprises about 50 mg to about 600 mg of the antibody or antigen-binding fragment thereof that binds IL-4R. In further embodiments, the pharmaceutical composition comprises about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg or about 300 mg of the antibody or fragment thereof that binds IL-4R.

[0027]

The invention includes a pharmaceutical composition comprising an anti-IL4R antibody antagonist or an antigen binding fragment thereof for use in the treatment and/or prevention of AD and related conditions.

[0034]

In some embodiments, the pharmaceutical composition comprises 75 mg to 600 mg of the anti-IL-4R antibody or antigen-binding fragment thereof. In one embodiment, the pharmaceutical composition comprises 300 mg of the anti-IL-4R antibody or fragment thereof.

[0043]

In one embodiment, the safe therapeutic dose is equal to or less than 500 mg. In one embodiment, the safe therapeutic dose is selected from the group consisting of 75 mg, 150 mg, and 300 mg.

[0048]

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this

invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (e.g., 99.1, 99.2, 99.3, 99.4, etc.). As used herein, the terms "treat", "treating", or the like, mean to alleviate symptoms, eliminate the causation of symptoms either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder or condition.

[0049]

The present invention includes methods which comprise administering to a subject in need thereof a therapeutic composition comprising an IL-4R antagonist. As used herein, the expression "a subject in need thereof" means a human or non-human animal that exhibits one or more symptoms or indicia of atopic dermatitis, and/or who has been diagnosed with atopic dermatitis. In certain embodiments, the methods of the present invention may be used to treat patients that show elevated levels of one or more AD-associated biomarkers (described elsewhere herein). For example, the methods of the present invention comprise administering an IL-4R antagonist to patients with elevated levels of IgE or TARC or periostin. In some embodiments, the methods herein may be used to treat AD in children who are ≤ 1 year old. For example, the present methods may be used to treat infants who are less than 1 month, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months or less than 12 months old. In other embodiments, the present methods may be used to treat children and/or adolescents who are ≤ 18 years old. For example, the present methods may be used to treat children or adolescents less than 17 years, 16 years, 15 years, 14 years, 13 years, 12 years, 11 years, 10 years, 9 years, 8 years, 7 years, 6 years, 5 years, 4 years, 3 years, or less than 2 years old.

[0050]

In the context of the present invention, "a subject in need thereof" may include, e.g., subjects who, prior to treatment, exhibit (or have exhibited) one or more AD-associated parameters such as, e.g., elevated IGA, BSA, EASI, SCORAD, 5D-Pruritus, and/or NRS score, and/or an elevated level of one or more AD-associated biomarker such as, e.g., IgE and/or TARC (as described elsewhere herein). In certain embodiments, "a subject in need thereof" may include a subset of population which is more susceptible to AD or may show an elevated level of an AD-associated biomarker. For example, "a subject in need thereof" may include a subset of population defined by a race or an ethnicity present in the population.

[0051]

"Atopic dermatitis" (AD), as used herein, means an inflammatory skin disease characterized by intense pruritus (e.g., severe itch) and by scaly and dry eczematous lesions. The term "atopic dermatitis" includes, but is not limited to, AD caused by or associated with epidermal barrier dysfunction, allergy (e.g., allergy to certain foods, pollen, mold, dust mite, animals, etc.), radiation exposure, and/or asthma. The present invention encompasses methods to treat patients with mild, moderate-to-severe or severe AD. As used herein, "moderate-to-severe AD", is characterized by intensely pruritic, widespread skin lesions that are often complicated by persistent bacterial, viral or fungal infections. Moderate-to-severe AD also includes chronic AD in patients. In many cases, the chronic lesions include thickened plaques of skin, lichenification and fibrous papules. Patients affected by moderate-to-severe AD also, in general, have more than 20% of the body's skin affected, or 10% of skin area in addition to involvement of the eyes, hands and body folds. Moderate-to-severe AD is also considered to be present in patients who require frequent treatment with topical corticosteroids. A patient may also be said to have moderate-to-severe AD when the patient is resistant or refractory to treatment by either a topical corticosteroid or a calcineurin inhibitor or any other commonly used therapeutic agent known in the art.

[0053]

The present invention includes methods to treat AD in patients resistant, non-responsive or inadequately responsive to treatment with a topical corticosteroid (TCS) or a calcineurin inhibitor. The term "resistant, non-responsive or inadequately responsive to a TCS or a calcineurin inhibitor", as used herein, refers to subjects or patients with AD who have been treated with a TCS or a calcineurin inhibitor and wherein the TCS/calcineurin inhibitor does not have a therapeutic effect. In some embodiments, the term refers to reduced patient compliance and/or toxicity and side effects and/or ineffectiveness of the administered TCS/calcineurin inhibitor to reduce, ameliorate or decrease the symptoms of AD. In some embodiments, the term refers to patients suffering from moderate-to-severe AD who are refractory to treatment by a TCS/calcineurin inhibitor. In some embodiments, the term refers to patients with AD which is uncontrolled despite treatment with a TCS and/or calcineurin inhibitor. In some embodiments, the patients who are "resistant, non-responsive or inadequately responsive to a TCS or a calcineurin inhibitor" may show no improvement in one or more AD-associated parameters. Examples of AD-associated parameters are described elsewhere herein. For example, treatment with a TCS/calcineurin inhibitor may result in no decrease in pruritus or EASI score or BSA score. In some embodiments, the present invention includes methods to treat moderate-to-severe AD in patients who have

been treated earlier with a TCS/calcineurin inhibitor for ≥ 1 month and do not show a decrease in one or more AD-associated parameters. For example, the present methods may be used to treat a patient with chronic AD who has been on a stable regimen of a TCS/calcineurin inhibitor and has a BSA score of ≥ 10% or an IGA score ≥ 3.

[0055]

The term "TCS", as used herein includes group I, group II, group III and group IV topical corticosteroids. According to the Anatomical Therapeutic Classification System of World Health Organization, the corticosteroids are classified as weak (group I), moderately potent (Group II) and potent (Group III) and very potent (Group IV), based on their activity as compared to hydrocortisone. Group IV TCS (very potent) are up to 600 times as potent as hydrocortisone and include clobetasol propionate and halcinonide. Group III TCS (potent) are 50 to 100 times as potent as hydrocortisone and include, but are not limited to, betamethasone valerate, betamethasone dipropionate, diflucortolone valerate, hydrocortisone-17-butyrate, mometasone furoate, and methylprednisolone aceponate. Group II TCS (moderately potent) are 2 to 25 times as potent as hydrocortisone and include, but are not limited to, clobetasone butyrate, and triamcinolone acetonide. Group I TCS (mild) includes hydrocortisone.

[0057]

Methods for Improving Atopic Dermatitis (AD)-Associated Parameters

The present invention includes methods for improving one or more atopic dermatitis (AD)-associated parameters in a subject in need thereof, wherein the methods comprise administering a pharmaceutical composition comprising an interleukin-4 receptor (IL-4R) antagonist to the subject.

[0058]

Examples of "AD-associated parameters" include: (a) Investigators Global Assessment (IGA); (b) Body Surface Area Involvement of Atopic Dermatitis (BSA); (c) Eczema Area and Severity Index (EASI); (d) SCORAD; (e) 5-D Pruritus Scale; and (f) Pruritus Numeric Rating Scale (NRS). An "improvement in an AD-associated parameter" means a decrease from baseline of one or more of IGA, BSA, EASI, SCORAD, 5-D Pruritus Scale, or NRS. As used herein, the term "baseline," with regard to an AD-associated parameter, means the numerical value of the AD-associated parameter for a subject prior to or at the time of administration of a pharmaceutical composition of the present invention.

[0059]

To determine whether an AD-associated parameter has "improved," the parameter is quantified at baseline and at one or more time points after administration of the

pharmaceutical composition of the present invention. For example, an AD-associated parameter may be measured at day 1, day 2, day 3, day 4, day 5, day 6, day 7, day 8, day 9, day 10, day 11, day 12, day 14, day 15, day 22, day 25, day 29, day 36, day 43, day 50, day 57, day 64, day 71, day 85; or at the end of week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, week 24, or longer, after the initial treatment with a pharmaceutical composition of the present invention. The difference between the value of the parameter at a particular time point following initiation of treatment and the value of the parameter at baseline is used to establish whether there has been an "improvement" (e.g., a decrease) in the AD associated parameter.

[0060]

Investigator's Global Assessment (IGA). The IGA is an assessment scale used in clinical settings to determine the severity of AD and clinical response to treatment based on a 6-point scale ranging from 0 (clear) to 5 (very severe). According to certain embodiments of the present invention, administration of an IL-4R antagonist to a patient results in a decrease in IGA score. For example, the present invention includes therapeutic methods which result in a decrease from baseline in IGA score of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85 or later following administration of the IL-4R antagonist (e.g., following subcutaneous administration of about 75 mg, 150 mg, or 300 mg of an anti-IL-4R antibody or antigen-binding fragment thereof). In certain exemplary embodiments of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in IGA of at least 25%. In one embodiment of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in IGA of at least 25% by day 15 after administration. In certain embodiments of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in IGA of at least 35% by day 22 after administration. In other embodiments, administration of an IL-4R antagonist to a subject results in a decrease from baseline in IGA of at least 40% or at least 45% through day 85 upon treatment.

[0061]

Body Surface Area Involvement of Atopic Dermatitis (BSA). BSA is assessed for each major section of the body (head, trunk, arms and legs) and is reported as a percentage of all major body sections combined. According to certain embodiments of the present invention, administration of an IL-4R antagonist to a patient results in a

decrease in BSA score. For example, the present invention includes therapeutic methods which result in a decrease from baseline in BSA score of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85 or later following administration of the IL-4R antagonist (e.g., following subcutaneous administration of about 75 mg, 150 mg, or 300 mg of an anti-IL-4R antibody or antigen-binding fragment thereof). In certain exemplary embodiments of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in BSA score of at least 35% after administration. In one embodiment of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in BSA score of at least 35% by day 29 after administration. In one embodiment of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in BSA score of at least 40% by day 29 after administration. In some embodiments, administration of an IL-4R antagonist to a subject results in a decrease from baseline in BSA score of at least 40% or at least 50% through day 85 upon treatment.

[0062]

Eczema Area and Severity Index (EASI). The EASI is a validated measure used in clinical settings to assess the severity and extent of AD. (Hanifin et al. 2001, Exp. Dermatol. 10: 11-18). Four AD disease characteristics are assessed for severity by a physician or other qualified medical professional on a scale of 0 (absent) through 3 (severe). In addition, the area of AD involvement is assessed as a percentage by body area of head, trunk, arms and legs and converted to a score of 0 to 6. According to certain embodiments of the present invention, administration of an IL-4R antagonist to a patient results in a decrease in EASI score. For example, the present invention includes therapeutic methods which result in a decrease from baseline in EASI score of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85 or later following administration of the IL-4R antagonist (e.g., following subcutaneous administration of about 75 mg, 150 mg, or 300 mg of an anti-IL-4R antibody or antigen-binding fragment thereof). In certain exemplary embodiments of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in EASI score of at least 45%. In one embodiment of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in EASI score of at least 45% by day 15 after administration. In one embodiment of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in EASI score of at least 50% by day 29 after administration. In some embodiments,

administration of an IL-4R antagonist to a subject results in a decrease from baseline in EASI score of at least 55% or at least 60% through day 85 upon treatment.

[0063]

SCORAD. SCORing Atopic Dermatitis (SCORAD) is a clinical assessment of the severity (e.g., extent or intensity) of atopic dermatitis developed by the European Task Force on Atopic Dermatitis (Consensus Report of the European Task Force on Atopic Dermatitis, 1993, Dermatology (Basel) 186(1): 23-31). The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The severity of 6 specific symptoms of AD is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the patient or relative on a visual analogue scale (VAS), where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: A/5 + 7B/2 + C. According to certain embodiments of the present invention, administration of an IL-4R antagonist to a patient results in a decrease in SCORAD score. For example, the present invention includes therapeutic methods which result in a decrease from baseline in SCORAD of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85 or later following administration of the IL-4R antagonist (e.g., following subcutaneous administration of about 75 mg, 150 mg, or 300 mg of an anti-IL-4R antibody or antigen-binding fragment thereof). In certain exemplary embodiments of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in SCORAD score of at least 30%. In one embodiment of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in SCORAD score of at least 30% by day 29 after administration. In one embodiment of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in SCORAD score of at least 35% by day 29 after administration. In some embodiments, administration of an IL-4R antagonist to a subject results in a decrease from baseline in SCORAD score of at least 40% or at least 45% through day 85 upon treatment.

[0064]

5-D Pruritus Scale. The 5-D Pruritus Scale is a 1-page, 5-question tool used in clinical settings to assess 5 dimensions of background itch: degree, duration, direction,

disability, and distribution. (Elman and Hynan, 2010, Brit. J. Dermatol. 162: 587-593). Each question corresponds to 1 of the 5 dimensions of itch; patients rate their symptoms as "present" or on a 1 to 5 scale, with 5 being the most affected. According to certain embodiments of the present invention, administration of an IL-4R antagonist to a patient results in a decrease in 5-D Pruritus Scale. For example, the present invention includes therapeutic methods which result in a decrease from baseline in 5-D Pruritus Scale of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at day 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85 or later following administration of the IL-4R antagonist (e.g., following subcutaneous administration of about 75 mg, 150 mg, or 300 mg of an anti-IL-4R antibody or antigen-binding fragment thereof). In certain exemplary embodiments of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in 5-D Pruritus Scale of at least 15%. In one embodiment of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in 5-D Pruritus Scale of at least 15% by day 15 after administration. In one embodiment of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in 5-D Pruritus Scale of at least 20% by day 15 after administration. In some embodiments, administration of an IL-4R antagonist to a subject results in a decrease from baseline in 5-D Pruritus Scale of at least 25% or at least 30% through day 85 upon treatment.

[0065]

Pruritus Numeric Rating Scale (NRS). The Pruritus NRS is a single-question assessment tool that is used to assess a subject's worst itch, on a scale of 1 to 10, as a result of AD in the previous 12 hours. According to certain embodiments of the present invention, administration of an IL-4R antagonist to a patient results in a decrease in NRS score. For example, the present invention includes therapeutic methods which result in a decrease from baseline in NRS score of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or more at the end of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or later following administration of the IL-4R antagonist (e.g., following subcutaneous administration of about 75 mg, 150 mg, or 300 mg of an anti-IL-4R antibody or antigen-binding fragment thereof). In certain exemplary embodiments of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in NRS score of at least 25%. In one embodiment of the present invention, administration of an IL-4R antagonist to a subject results in a decrease from baseline in NRS score of at least 25% by the end of week 2 after administration. In one embodiment of the present invention, administration of an

IL-4R antagonist to a subject results in a decrease from baseline in NRS score of at least 30% by the end of week 2 after administration. In some embodiments, administration of an IL-4R antagonist to a subject results in a decrease from baseline in NRS score of at least 45% or at least 50% through day 85 upon treatment.

[0084]

Atopic Dermatitis-Associated Biomarkers

The present invention also includes methods involving the use, quantification, and analysis of AD-associated biomarkers. As used herein, the term "AD-associated biomarker" means any biological response, cell type, parameter, protein, polypeptide, enzyme, enzyme activity, metabolite, nucleic acid, carbohydrate, or other biomolecule which is present or detectable in an AD patient at a level or amount that is different from (e.g., greater than or less than) the level or amount of the marker present or detectable in a non-AD patient. In some embodiments, the term "AD-associated biomarker" includes a biomarker associated with Type 2 helper T-cell (Th2)-driven inflammation. Exemplary AD-associated biomarkers include, but are not limited to, e.g., thymus and activation-regulated chemokine (TARC; also known as CCL17), immunoglobulin E (IgE), eotaxin-3 (also known as CCL26), lactate dehydrogenase (LDH), eosinophils, antigen-specific IgE (e.g., Phadiatop™ test), and periostin. The term "AD-associated biomarker" also includes a gene or gene probe known in the art which is differentially expressed in a subject with AD as compared to a subject without AD. For example, genes which are significantly up-regulated in a subject with AD include, but are not limited to, T-helper 2 (Th2)-associated chemokines such as CCL13, CCL17, CCL18 and CCL26, markers of epidermal proliferation such as K16, Ki67, and T-cell and dendritic cell antigens CD2, CD1b, and CD1c (Tintle et al 2011; J. Allergy Clin. Immunol. 128: 583-593). Alternatively, "AD-associated biomarker" also includes genes which are down regulated due to AD such as terminal differentiation proteins (e.g., loricrin, filaggrin and involucrin) (Tintle et al 2011; J. Allergy Clin. Immunol. 128: 583-593). Certain embodiments of the invention pertain to use of these biomarkers for monitoring disease reversal with the administration of the IL-4R antagonist. Methods for detecting and/or quantifying such AD-associated biomarkers are known in the art; kits for measuring such AD-associated biomarkers are available from various commercial sources; and various commercial diagnostic laboratories offer services which provide measurements of such biomarkers as well.

[0085]

According to certain aspects of the invention, methods for treating AD are provided which comprise: (a) selecting a subject who exhibits a level of at least one AD-

associated biomarker prior to or at the time of treatment which signifies the disease state; and (b) administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an IL-4R antagonist. In certain embodiments, the patient is selected by determining if the level of an AD-associated biomarker is elevated. The level of an AD-associated biomarker is determined or quantified by acquiring a sample from the patient for a biomarker assay known in the art. In certain other embodiments, a patient is selected by acquiring information relating to an elevated level of an AD-associated biomarker from the patient. In certain embodiments of this aspect of the invention, the subject is selected on the basis of an elevated level of IgE or TARC or periostin.

[0086]

For purposes of the present invention, a normal IgE level in healthy subjects is less than about 114 kU/L (e.g., as measured using the ImmunoCAP® assay [Phadia, Inc. Portage, Ml]). Thus, the present invention involves methods comprising selecting a subject who exhibits a serum IgE level greater than about 114 kU/L, greater than about 150 kU/L, greater than about 500 kU/L, greater than about 1000 kU/L, greater than about 1500 kU/L, greater than about 2000 kU/L, greater than about 2500 kU/L, greater than about 3000 kU/L, greater than about 3500 kU/L, greater than about 4000 kU/L, greater than about 4500 kU/L, or greater than about 5000 kU/L, and administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an IL-4R antagonist.

[0087]

TARC levels in healthy subjects are in the range of 106 ng/L to 431 ng/L, with a mean of about 239 ng/L. (An exemplary assay system for measuring TARC level is the TARC quantitative ELISA kit offered as Cat. No. DDN00 by R&D Systems, Minneapolis, MN.) Thus, the present invention involves methods comprising selecting a subject who exhibits a serum TARC level greater than about 431 ng/L, greater than about 500 ng/L, greater than about 1000 ng/L, greater than about 1500 ng/L, greater than about 2000 ng/L, greater than about 2500 ng/L, greater than about 3000 ng/L, greater than about 3500 ng/L, greater than about 4000 ng/L, greater than about 4500 ng/L, or greater than about 5000 ng/L, and administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an IL-4R antagonist.

[0088]

Another AD-associated biomarker is antigen-specific IgE. Phadiatop™ is a commercially available variant of serum specific or antigen-specific IgE assay test that was introduced for the screening of allergic sensitization (Merrett et al 1987, Allergy

17: 409-416). The test provides for simultaneous testing for serum specific IgE to a mixture of relevant allergens causing common inhalant allergies. The test gives a qualitative result, either positive or negative depending upon a fluorescence response obtained. When a patient sample gives a fluorescence response higher than or equal to the reference, a positive test result is indicated. A patient sample with a lower fluorescence response indicates a negative test result. The present invention includes methods comprising selecting a subject who exhibits a positive test result and administering to the subject a therapeutically effective amount of an IL-4R antagonist.
[0089]

Periostin is an extracellular matrix protein involved in the Th2-mediated inflammatory processes. Periostin levels are found to be up regulated in patients with AD (Masuoka et al 2012 J Clin Invest. 122(7): 2590-2600. doi: 10.1172/JCI58978). The present invention includes methods comprising administering an IL-4R antagonist to treat patients with elevated levels of periostin.
[0090]

Lactate dehydrogenase (LDH) is used as a marker of tissue damage and is found to be elevated in patients with AD (Kou et al 2012; Arch. Dermatol. Res. 304: 305-312). The present invention includes methods comprising administering an IL-4R antagonist to treat patients with elevated levels of LDH.
[0091]

According to other aspects of the invention, methods for treating AD are provided which comprise administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of an IL-4R antagonist, wherein administration of the pharmaceutical composition to the subject results in a decrease in at least one AD-associated biomarker (e.g., IgE, TARC, eosinophils, eotaxin-3, antigen-specific IgE, LDH, etc.) at a time after administration of the pharmaceutical composition, as compared to the level of the biomarker in the subject prior to the administration.
[0092]

As will be appreciated by a person of ordinary skill in the art, an increase or decrease in an AD-associated biomarker can be determined by comparing (i) the level of the biomarker measured in a subject at a defined time point after administration of the pharmaceutical composition comprising an IL-4R antagonist to (ii) the level of the biomarker measured in the patient prior to the administration of the pharmaceutical composition comprising an IL-4R antagonist (i.e., the "baseline measurement"). The defined time point at which the biomarker is measured can be, e.g., at about 4 hours, 8 hours, 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10

days, 15 days, 20 days, 35 days, 40 days, 50 days, 55 days, 60 days, 65 days, 70 days, 75 days, 80 days, 85 days, or more after administration of the of the pharmaceutical composition comprising an IL-4R antagonist.

[0096]

Interleukin-4 Receptor Antagonists

As disclosed in detail above, the present invention includes methods which comprise administering to a subject in need thereof a therapeutic composition comprising an interleukin-4 receptor (IL-4R) antagonist. As used herein, an "IL-4R antagonist" is any agent which binds to or interacts with IL-4R and inhibits the normal biological signaling function of IL-4R when IL-4R is expressed on a cell in vitro or in vivo. Non-limiting examples of categories of IL-4R antagonists include small molecule IL-4R antagonists, anti-IL-4R aptamers, peptide-based IL-4R antagonists (e.g., "peptibody" molecules), and antibodies or antigen-binding fragments of antibodies that specifically bind human IL-4R.

[0097]

The terms "IL-4R," "hlL-4R," and the like, as used herein, are intended to refer to the alpha chain of the human cytokine receptor that specifically binds interleukin-4 (IL-4), IL-4Ra (SEQ ID NO: 274). Unless specifically designated as being from a non-human species, the term "IL-4R", as used herein, shall be understood to mean the human interleukin-4 receptor alpha chain.

[0098]

The term "antibody," as used herein, is intended to refer to immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, as well as multimers thereof (e.g., IgM). Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region comprises three domains, C_H1, C_H2 and C_H3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region comprises one domain (C_L1). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In different embodiments of the invention, the FRs of the anti-IL-4R antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus

sequence may be defined based on a side-by-side analysis of two or more CDRs.
[0099]

The term "antibody," as used herein, also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, e.g., from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, e.g., commercial sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.
[0100]

Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (e.g. monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.
[0105]

The term "human antibody," as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may nonetheless include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs and in particular CDR3. However, the term "human antibody," as used herein, is not intended to include antibodies in which CDR sequences derived from

the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0106]

The term "recombinant human antibody," as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor et al. (1992) Nucl. Acids Res. 20: 6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire in vivo.

[0110]

The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Methods for determining whether an antibody specifically binds to an antigen are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. For example, an antibody that "specifically binds" IL-4R, as used in the context of the present invention, includes antibodies that bind IL-4R or portion thereof with a KD of less than about 1000 nM, less than about 500 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 90 nM, less than about 80 nM, less than about 70 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, less than about 1 nM or less than about 0.5 nM, as measured in a surface plasmon resonance assay. An isolated antibody that specifically binds human IL-4R may, however, have cross-reactivity to other antigens, such as IL-4R molecules from other (non-human) species.

[0111]

The anti-IL-4R antibodies useful for the methods of the present invention may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences from which the antibodies were derived. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present invention includes methods involving the use of antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as "germline mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V_H and/or V_L domains are mutated back to the residues found in the original germline sequence from which the antibody was derived. In other embodiments, only certain residues are mutated back to the original germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (i.e., a germline sequence that is different from the germline sequence from which the antibody was originally derived). Furthermore, the antibodies of the present invention may contain any combination of two or more germline mutations within the framework and/or CDR regions, e.g., wherein certain individual residues are mutated to the corresponding residue of a particular germline sequence while certain other residues that differ from the original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies and antigen-binding fragments that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. The use of antibodies and antigen-binding fragments obtained in

this general manner are encompassed within the present invention.

[0112]

The present invention also includes methods involving the use of anti-IL-4R antibodies comprising variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present invention includes the use of anti-IL-4R antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein.

[0114]

The term "KD," as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0115]

The term "epitope" refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

[0116]

Preparation of Human Antibodies

Methods for generating human antibodies in transgenic mice are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to human IL-4R.

[0117]

Using VELOCIMMUNE™ technology (see, for example, US 6,596,541, Regeneron Pharmaceuticals) or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to IL-4R are initially isolated having a human variable region and a mouse constant region. The VELOCIMMUNE® technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable

regions of the heavy and light chains of the antibody are isolated and operably linked to DNA encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody.

[0118]

Generally, a VELOCIMMUNE® mouse is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

[0119]

Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. The antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc., using standard procedures known to those skilled in the art. The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified lgG1 or lgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[0120]

In general, the antibodies that can be used in the methods of the present invention possess high affinities, as described above, when measured by binding to antigen either immobilized on solid phase or in solution phase. The mouse constant regions are replaced with desired human constant regions to generate the fully human antibodies of the invention. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[0121]

Specific examples of human antibodies or antigen-binding fragments of antibodies that specifically bind IL-4R which can be used in the context of the methods of the present invention include any antibody or antigen-binding fragment which comprises

the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 22, 26, 42, 46, 50, 66, 70, 74, 90, 94, 98, 114, 118, 122, 138, 142, 146, 162, 166, 170, 186, 190, 194, 210, 214, 218, 234, 238, 242, 258 and 262. The antibody or antigen-binding fragment may comprise the three light chain CDRs (LCVR1, LCVR2, LCVR3) contained within a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 20, 24, 34, 44, 48, 58, 68, 72, 82, 92, 96, 106, 116, 120, 130, 140, 144, 154, 164, 168, 178, 188, 192, 202, 212, 216, 226, 236, 240, 250, 260 and 264. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, e.g., the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. See, e.g., Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani et al., J. Mol. Biol. 273: 927-948 (1997); and Martin et al., Proc. Natl. Acad. Sci. USA 86: 9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[0122]

In certain embodiments of the present invention, the antibody or antigen-binding fragment thereof comprises the six CDRs (HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3) from the heavy and light chain variable region amino acid sequence pairs (HCVR/LCVR) selected from the group consisting of SEQ ID NOs: 2/10, 18/20, 22/24, 26/34, 42/44, 46/48, 50/58, 66/68, 70/72, 74/82, 90/92, 94/96, 98/106, 114/116, 118/120, 122/130, 138/140, 142/144, 146/154, 162/164, 166/168, 170/178, 186/188, 190/192, 194/202, 210/212, 214/216, 218/226, 234/236, 238/240, 242/250, 258/260 and 262/264.

[0123]

In certain embodiments of the present invention, the antibody or antigen-binding fragment thereof comprises six CDRs (HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3) having the amino acid sequences selected from the group consisting of SEQ ID NOs: 4/6/8/12/14/16; 28/30/32/36/38/40; 52/54/56/60/62/64; 76/78/80/84/86/88; 100/102/104/108/110/112; 124/126/128/132/134/136; 148/150/152/156/158/160; 172/174/176/180/182/184;

196/198/200/204/206/208; 220/222/224/228/230/232; and 244/246/248/252/254/256.

[0124]

In certain embodiments of the present invention, the antibody or antigen-binding fragment thereof comprises HCVR/LCVR amino acid sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/20, 22/24, 26/34, 42/44, 46/48, 50/58, 66/68, 70/72, 74/82, 90/92, 94/96, 98/106, 114/116, 118/120, 122/130, 138/140, 142/144, 146/154, 162/164, 166/168, 170/178, 186/188, 190/192, 194/202, 210/212, 214/216, 218/226, 234/236, 238/240, 242/250, 258/260 and 262/264.

[0125]

Pharmaceutical Compositions

The present invention includes methods which comprise administering an IL-4R antagonist to a patient, wherein the IL-4R antagonist is contained within a pharmaceutical composition. The pharmaceutical compositions of the invention are formulated with suitable carriers, excipients, and other agents that provide suitable transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN^{TM}), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52: 238-311.

[0126]

The dose of antibody administered to a patient according to the methods of the present invention may vary depending upon the age and the size of the patient, symptoms, conditions, route of administration, and the like. The dose is typically calculated according to body weight or body surface area. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. Effective dosages and schedules for administering pharmaceutical compositions comprising anti-IL-4R antibodies may be determined empirically; for example, patient progress can be monitored by periodic assessment, and the dose adjusted accordingly. Moreover, interspecies scaling of dosages can be performed using well-known methods in the art (e.g., Mordenti et al., 1991, Pharmaceut. Res. 8: 1351). Specific exemplary doses of anti-IL4R antibodies, and administration regimens involving the same, that can be used in the context of the present invention are disclosed elsewhere herein.

[0127]

Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al., 1987, J. Biol. Chem. 262: 4429-4432). Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents.

[0128]

A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0131]

The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by known methods. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50

(polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared can be filled in an appropriate ampoule.

[0132]

Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc.

[0133]

Exemplary pharmaceutical compositions comprising an anti-IL-4R antibody that can be used in the context of the present invention are disclosed, e.g., in US Patent Application Publication No. 2012/0097565.

[0134]

Dosage

The amount of IL-4R antagonist (e.g., anti-IL-4R antibody) administered to a subject according to the methods of the present invention is, generally, a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means an amount of IL-4R antagonist that results in one or more of: (a) an improvement in one or more AD-associated parameters (as defined elsewhere herein); and/or (b) a detectable improvement in one or more symptoms or indicia of atopic dermatitis. A "therapeutically effective amount" also includes an amount of IL-4R antagonist that inhibits, prevents, lessens, or delays the progression of AD in a subject.

[0135]

In the case of an anti-IL-4R antibody, a therapeutically effective amount can be from about 0.05 mg to about 600 mg, e.g., about 0.05 mg, about 0.1 mg, about 1.0 mg, about 1.5 mg, about 2.0 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about

560 mg, about 570 mg, about 580 mg, about 590 mg, or about 600 mg, of the anti-IL-4R antibody. In certain embodiments, 75 mg, 150 mg, or 300 mg of an anti-IL-4R antibody is administered to a subject.

[0136]

The amount of IL-4R antagonist contained within the individual doses may be expressed in terms of milligrams of antibody per kilogram of patient body weight (i.e., mg/kg). For example, the IL-4R antagonist may be administered to a patient at a dose of about 0.0001 to about 10 mg/kg of patient body weight.

[0141]

Administration Regimens

The present invention includes methods comprising administering to a subject a pharmaceutical composition comprising an IL-4R antagonist at a dosing frequency of about four times a week, twice a week, once a week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every eight weeks, once every twelve weeks, or less frequently so long as a therapeutic response is achieved. In certain embodiments involving the administration of a pharmaceutical composition comprising an anti-IL-4R antibody, once a week dosing at an amount of about 75 mg, 150 mg, or 300 mg, can be employed.

[0142]

According to certain embodiments of the present invention, multiple doses of an IL-4R antagonist may be administered to a subject over a defined time course. The methods according to this aspect of the invention comprise sequentially administering to a subject multiple doses of an IL-4R antagonist. As used herein, "sequentially administering" means that each dose of IL-4R antagonist is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the patient a single initial dose of an IL-4R antagonist, followed by one or more secondary doses of the IL-4R antagonist, and optionally followed by one or more tertiary doses of the IL-4R antagonist.

[0143]

The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the IL-4R antagonist. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same

amount of IL-4R antagonist, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of IL-4R antagonist contained in the initial, secondary and/or tertiary doses varies from one another (e.g., adjusted up or down as appropriate) during the course of treatment. In certain embodiments, one or more (e.g., 1, 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (e.g., "maintenance doses"). For example, an IL-4R antagonist may be administered to a patient with AD at a loading dose of about 300 mg or about 600 mg followed by one or more maintenance doses of about 75 mg to about 300 mg. In one embodiment, the initial dose and the one or more secondary doses each include 50 mg to 600 mg of the IL-4R antagonist, e.g., 100 mg to 400 mg of the IL-4R antagonist, e.g., 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg or 500 mg of the IL-4R antagonist. In some embodiments, the initial dose and the one or more secondary doses each contain the same amount of the IL-4R antagonist. In other embodiments, the initial dose comprises a first amount of the IL-4R antagonist, and the one or more secondary doses each comprise a second amount of the IL-4R antagonist. For example, the first amount of the IL-4R antagonist can be 1.5×, 2×, 2.5×, 3×, 3.5×, 4× or 5× or more than the second amount of the IL-4R antagonist.

[Examples]

[0153]

[Example 1]

Generation of Human Antibodies to Human IL-4R

Human anti-hlL-4R antibodies were generated as described in US Patent No. 7,608,693. Table 1 sets forth the sequence identifiers for the heavy and light chain variable region amino acid sequence pairs, and CDR amino acid sequences, of selected anti-IL-4R antibodies and their corresponding antibody designations.

[0154]

[Table 1]

Table 1

	SEQ ID NOs:							
Antibody Designation	HCVR	HCDR1	HCDR2	HCDR3	LCVR	LCDR1	LCDR2	LCDR3
H1H095-a	2	4	6	8	10	12	14	16
H1H095-b	18	4	6	8	20	12	14	16
H1H095-c	22	4	6	8	24	12	14	16
H1H097-a	26	28	30	32	34	36	38	40
H1H097-b	42	28	30	32	44	36	38	40
H1H097-c	46	28	30	32	48	36	38	40
H1H093-a	50	52	54	56	58	60	62	64
H1H093-b	66	52	54	56	68	60	62	64
H1H093-c	70	52	54	56	72	60	62	64
H1H093-d	74	76	78	80	82	84	86	88
H1H093-e	90	76	78	80	92	84	86	88
H1H093-f	94	76	78	80	96	84	86	88
H1H094-a	98	100	102	104	106	108	110	112
H1H094-b	114	100	102	104	116	108	110	112
H1H094-c	118	100	102	104	120	108	110	112
H1H096-a	122	124	126	128	130	132	134	136
H1H096-b	138	124	126	128	140	132	134	136
H1H096-c	142	124	126	128	144	132	134	136
H1H098-a	146	148	150	152	154	156	158	160
H1H098-b	162	148	150	152	164	156	158	160
H1H098-c	166	148	150	152	168	156	158	160
H1H099-a	170	172	174	176	178	180	182	184
H1H099-b	186	172	174	176	188	180	182	184
H1H099-c	190	172	174	176	192	180	182	184
H4H083-a	194	196	198	200	202	204	206	208
H4H083-b	210	196	198	200	212	204	206	208
H4H083-c	214	196	198	200	216	204	206	208
H4H121-a	218	220	222	224	226	228	230	232

[0155]

[Table 2]

H4H121-b	234	220	222	224	236	228	230	232
H4H121-c	238	220	222	224	240	228	230	232
H4H118-a	242	244	246	248	250	252	254	256
H4H118-b	258	244	246	248	260	252	254	256
H4H118-c	262	244	246	248	264	252	254	256

[0156]

The exemplary IL-4R antagonist used in the following Examples is the human anti-IL-4R antibody designated in Table 1 as H1H098-b (also referred to herein as "mAb1").

[0241]

[Example 6]

Sequential Ascending repeat-dose clinical trial of subcutaneously administered anti-IL-4R antibody (mAb1) in patients with moderate-to-severe atopic dermatitis

A. Study Design

This study was a phase 1b, randomized, double-blind, placebo-controlled, sequential ascending, repeat-dose study of mAb1 subcutaneously administered in patients with moderate-to-severe extrinsic atopic dermatitis (AD). Thirty patients were randomized into the study (6 in placebo, 8 each in of 75 mg, 150 mg and 300 mg groups). Twenty-eight patients received all the treatments. The treatment period was 4 weeks in duration; patients were followed for 8 weeks after end of the treatment period. Patients were randomized in a 4:1 ratio to receive mAb1 or placebo in each of 3 ascending dose cohorts (75, 150, or 300 mg mAb1). The primary objective of the trial was to access the safety and tolerability, with PK as a secondary objective. Exploratory objectives included efficacy and biomarker endpoints. The exploratory efficacy variables included: (i) proportion of patients who achieved an IGA score of 0 or 1 through week 4 and each study visit; (ii) change and percent change in BSA, EASI, and 5-D pruritus scale from baseline to each visit; and (iii) weekly change from baseline in NRS scale.

[0253]

E. Results

Subcutaneous administration of mAb1 to patients with moderate-to-severe AD was safe and well tolerated in this study. A single serious adverse event was recorded for a patient in the 150 mg group, who was diagnosed with exercise-associated CPK increase. No deaths were reported. 25 of the treated patients or 83% reported at least one treatment emergent adverse event (TEAE). The most frequent TEAE from the treatment

groups were infections and infestations (n = 7 [29%] vs. 1 [17%] for placebo), and headaches in patients dosed with mAb1 (n = 3 [13%] vs. 1 [17%] for placebo).

[0254]

The baseline and exploratory efficacy results obtained from the study are summarized in Figures 3 - 14. mAb1 administration did not induce statistically significant improvement in any exploratory endpoints of AD. This may be due to the small sample size and the fact that the placebo patients were less severe and younger than active treatment groups.

[0255]

[Example 7]

Clinical Trial of Subcutaneously Administered Anti-IL-4R Antibody (mAb1) In Patients with Moderate-to-Severe Atopic Dermatitis

A. Study Design

This study was a 12-week, double-blind, randomized, placebo-controlled, sequential ascending, repeated-dose study to assess the safety and pharmacokinetic profile of subcutaneous administration of the anti-IL-4R mAb, referred to herein as "mAb1," in adult patients with moderate-to-severe atopic dermatitis. Patients with moderate-to-severe AD had an Eczema Area and Severity Index (EASI) ≥ 12 and minimum 10% body surface area involvement. The treatment period was four weeks in duration, with patients being followed for 8 weeks after the end of the treatment period. Patients were withdrawn from topical agents (e.g., pimecrolimus, tacrolimus, and topical corticosteroids) for at least 1 week prior to baseline. Oral corticosteroids and immunosuppressives (e.g., cyclosporine, mycophenolate-mofetil, IFNy) were also prohibited from ≥ 4 weeks prior to baseline.

[0297]

F. Conclusions

Subcutaneous administration of an anti-IL-4R antibody (mAb1) to adult patients with moderate-to-severe atopic dermatitis was generally safe and well tolerated after 4 weekly doses of 150 or 300 mg with an adverse event (AE) rate similar to placebo and no dose limiting toxicities or serious AEs. The most common AEs with mAb1 were nasopharyngitis and headache. The mAb1 rapidly (by Day 8) reduced pruritus and improved skin disease in a dose-dependent fashion. Administration of mAb1 at 150 and 300 mg resulted in significant improvement in IGA, EASI, BSA, SCORAD and NRS pruritus as early as Day 8 through day 85 in both mean and absolute and percent change, as compared to baseline (see Tables 9 - 14). In the 300 mg arm at day 29, proportion of patients who achieved an EASI50 response was 71.4% vs 18.8% for placebo (p =

0.0025) and NRS pruritus score decreased by 45.4% vs 18.6% for placebo ($p = 0.0016$). The effect was sustained through day 85 for EASI50 and day 75 for NRS pruritus. For the 300 mg treatment group, the difference from placebo was significant for an additional 6 weeks after end of treatment period. The mAb significantly improved other clinical outcomes at day 29, mean % change IGA ($p = 0.0002$), EASI ($p < 0.0001$), BSA ($p = 0.0037$), and 5D pruritus ($p < 0.0001$). These improvements were generally observed by Day 8 and persisted after end of treatment. No rebound phenomena were observed after end of treatment.

[0298]

The results shown in this Example therefore demonstrate that mAb1 is safe and effective for the treatment of atopic dermatitis.

[0299]

[Example 8]

Treatment of patients with moderate-to-severe atopic dermatitis with anti-IL-4R antibody: analysis of pooled phase 1b studies

AD efficacy parameters were measured and pooled for analysis from two separate clinical trials in patients with moderate-to-severe AD. "Study A" was a 12-week, double-blind, randomized, placebo-controlled, sequential ascending dose study to assess the safety and tolerability of administered anti-IL-4R antibody (mAb1) in patients with atopic dermatitis. The treatment period was 4 weeks with patients being followed for 8 weeks after the end of the treatment period. Patients were randomized in a 4:1 ratio to receive mAb1 or placebo in each of the three ascending dose cohorts (75 mg, 150 mg, or 300 mg). The study consisted of a screening period (day -14 to day -3), a treatment period (day 1 through day 29), and a follow-up period (day 29 through day 85). During the treatment period, patients were seen in the clinic once weekly for safety, laboratory and clinical effect assessments on days 1, 4, 8, 15, 22, 25 and 29 (week 4). Patients received a dose of mAb1 or placebo on days 1, 8, 15 and 22. The end of the treatment period study was on day 29 (week 4). Patients were monitored at the study site for 6 hours after the injection (of mAb1 or placebo) on day 1, and for 3 hours after the injection on days 8, 15 and 22. During the follow-up period, patients were seen in the clinic for follow-up assessments at days 36, 43, 50, 57, 64, 71, and 85 (end of study visit).

[0300]

"Study B" was a 12-week, double-blind, randomized, placebo-controlled, sequential ascending, repeated-dose study in patients with moderate-to-severe AD. AD subjects were administered 150 mg or 300 mg of mAb1, or placebo on days 1, 8, 15 and 22 of

the study (four weekly doses) (See Example 3 herein). All administrations for both studies were subcutaneous.

[0301]

The patient inclusion criteria for the studies were: (1) should be male or female ≥ 18 years; (2) have chronic atopic dermatitis for 3 years; (3) have EASI ≥ 12; (4) IGA ≥ 3; (5) ≥ 15% BSA of AD involvement (in the US) or ≥ 10% BSA of AD involvement (ex-US); and (6) history of inadequate response to stable regimen of topical corticosteroids (TCS) or calcineurin inhibitors.

[0302]

The patient exclusion criteria for the study were: (1) WBC < 3.5 × 10^3/μI; (2) platelets < 125 × 10^3/μI; (3) neutrophils < 1.75 × 10^3/μI; (4) AST/ALT > 1.5× ULN; (5) positive for hepatitis B or hepatitis C; and (6) treatment with TCS or calcineurin inhibitors within 1 week of baseline.

[0303]

The primary endpoint of the studies was to monitor incidence of treatment-emergent adverse events (TEAEs) from baseline through week 12. The exploratory endpoints for efficacy variables were: (i) % achieving an IGA of 0 or 1 through week 4; (ii) % improvement in BSA and EASI from baseline; and (iii) change from baseline in NRS scale.

[0304]

The efficacy variables IGA, BSA, EASI, SCORAD, 5-D Pruritus scale, and Pruritus NRS rating have been described elsewhere herein (see, e.g., Example 4).

[0305]

The IGA, BSA, EASI and SCORAD scores were assessed at every clinic visit. Patients underwent 5-D pruritus assessment at the following visits: screening, day 1/baseline (pre-dose), and days 15, 29, 43, 57, 71, and 85 (end of study) or early termination. Patients used the IVRS to record their Pruritus NRS score twice daily through the last study visit.

[0306]

Baseline for efficacy variable is defined as the last non-missing value on or before the date of randomization. For the patient who has no value on or before his/her randomization date the last non-missing value on or before the date of first dose injection will be used as baseline.

[0307]

The baseline demographics for the patient population are presented below in Table 15.

[Table 21]

Table 15: Baseline Demographics

	Placebo (N=16)	75 mg (N=8)	150mg (N=22)	300mg (N=21)	All Doses (N=51)
Mean age, years (SD)	37.4 (17.16)	35.8 (12.51)	42.5 (11.37)	45.4 (15.92)	42.6 (13.73)
Race, n (%)					
Caucasian	13 (81.3%)	4 (50.0%)	19 (86.4%)	16 (76.2%)	39 (76.5%)
Non-Caucasian	3 (18.7%)	4 (50.0%)	3 (13.6%)	5 (23.8%)	12 (23.5%)
Gender, n (%)					
Male	11 (68.8%)	6 (75.0%)	12 (54.5%)	10 (47.6%)	28 (54.9%)
Female	5 (31.3%)	2 (25.0%)	10 (45.5%)	11 (52.4%)	23 (45.1%)
Mean BMI, kg/m^3 (SD)	25.69 (5.993)	26.41 (4.489)	25.68 (3.991)	27.71 (8.667)	26.63 (6.361)

[0308]

The mean baseline disease characteristics are given in Table 16.

[Table 22]

Table 16: Mean Baseline Disease Characteristics

	Placebo (N=16)	75 mg (N=8)	150mg (N=22)	300mg (N=21)	All Doses (N=51)
Duration of chronic AD, years	31.8 (18.67)	24.5 (16.95)	32.1 (15.44)	30.7 (16.95)	30.4 (16.19)
EASI score	22.8 (12.02)	36.9 911.75)	30.0 (17.00)	27.4 (11.21)	30.0 (14.19)
IGA score	3.6 (0.72)	4.1 (0.35)	3.9 (0.68)	3.5 (0.51)	3.8 (0.62)
%BSA of AD	40.3 (25.77)	64.4 917.03)	49.8 (28.75)	48.2 (22.26)	51.4 (24.87)
5-D pruritus scale	16.9 (3.94)	21.5 (3.55)	19.0 (2.94)	18.7 (3.64)	19.3 (3.41)
Pruritus NRS score	5.8 (1.75)	7.0 (1.78)	6.0 (1.82)	5.7 (1.51)	6.0 (1.72)

[0309]

The exploratory efficacy results obtained from the pooled studies are summarized in Table 17 and in Figures 15 - 22.

[0310]

[Table 23]

Table 17: Summary of subjects achieving IGA < 1 at Day 29 and all study visits

Number and % subjects with IGA≤ 1	Placebo (N=16)	75 mg (N=8)	150 mg (N=22)	300 mg (N=21)	All Doses Combined (N=51)
Week 4, Day 29	1 (6.3%)	0	4 (18.2%)	2 (9.5%)	6 (11.8%)
Day 4	0	0	0	0	0
Week 1, Day 8	0	0	0	0	0
Week 2, Day 15	0	0	0	1 (4.8%)	1 (2.0%)
Week 3, Day 22	0	0	0	2 (9.5%)	2 (3.9%)
Week 3, Day 25	1 (6.3%)	0	1 (4.5%)	4 (19.0%)	5 (9.8%)
Week 5, Day 36	1	0	4 (18.2%)	2 (9.5%)	6 (11.8%)
Week 6, Day 43	2 (12.5%)	0	5 (22.7%)	3 (14.3%)	8 (15.7%)
Week 7, Day 50	2 (12.5%)	0	4 (18.2%)	3 (14.3%)	7 (13.7%)
Week 8, Day 57	2 (12.5%0	0	3 (13.6%)	5 (23.8%)	8 (15.7%)
Week 9, Day 64	1 (6.3%)	0	3 (13.6%)	4 (19.0%)	7 (13.7%)
Week 10, Day 71	1 (6.3%)	0	1 (4.5%)	5 (23.8%)	6 (11.8%)
Week 12, Day 85	1 (6.3%)	0	0	3 (14.3%)	3 (5.9%)

[0311]
[Table 24]

Table 18: Summary of Percentage and Absolute Change in BSA Score from Baseline - all values represented as Mean (SD)

		mAb1			
	Placebo	**75mg**	**150mg**	**300mg**	**All Doses Combined**
No. Patients	16	8	22	21	51
Baseline BSA Score	40.3 (25.77)	64.4 (17.03)	49.8 (28.75)	48.2 (22.26)	51.4 (24.87)
Day **15** BSA Score	37.6 (26.61)	52.3 (12.54)	40.9 (25.66)	34.4 (22.66)	40.0 (23.23)
% Change from Baseline to Day **15**	-4.8 (14.80)	-16.8 (15.17)	-13.9 (21.77)	-30.5 (27.09)	-21.4 (24.27)
Absolute change from Baseline to Day **15**	-1.7 (5.37)	-12.1 (11.58)	-7.0 (15.07)	-13.9 (14.73)	-10.7 (14.51)
Day **29** BSA Score	31.1 (29.69)	46.3 (12.42)	31.1 (28.78)	31.5 925.33)	33.8 (25.47)
% Change from Baseline to Day **29**	-15.3 (31.02)	-26.4 (16.41)	-38.8 (37.00)	-40.3 (33.78)	-37.4 (32.88)
Absolute change from Baseline to Day **29**	-2.1 (10.93)	-18.1 (13.14)	-18.2 (24.61)	-16.7 (16.05)	-17.5 (19.31)
Day **36** BSA Score	25.1 (26.81)	41.2 (15.59)	24.9 (24.15)	26.0 (22.67)	28.0 (22.70)
% Change from Baseline to Day **36**	-13.3 (39.22)	-33.7 (21.53)	-48.6 (32.13)	-44.2 (34.61)	-44.4 (31.41)
Absolute change from Baseline to Day **36**	-1.8 (10.33)	-22.4 (15.26)	-24.3 (25.07)	-18.0 (17.82)	-21.6 (20.85)
Day **43** BSA Score	29.9 (27.04)	48.4 (21.56)	24.8 (26.36)	26.2 (21.03)	29.1 (24.42)
% Change from Baseline to Day **43**	-11.0 (39.52)	-29.2 (24.87)	-43.3 (42.81)	-47.2 (30.07)	-42.7 (35.05)
Absolute change from Baseline to Day **43**	-2.0 (10.74)	-19.0 (15.63)	-22.2 (29.35)	-19.8 (14.41)	-20.7 (21.52)
Day **57** BSA Score	27.2 (31.12)	57.5 (23.40)	31.2 (28.60)	28.3 (20.11)	33.7 (26.24)
% Change from Baseline to Day **57**	-33.6 (32.95)	-18.7 (23.06)	-37.4 (42.74)	-41.9 (29.38)	-36.6 (35.90)
Absolute change from Baseline to Day **57**	-8.3 (16.62)	-12.4 (16.36)	-20.0 (28.38)	-17.6 (13.86)	-18.0 (21.99)
Day **71** BSA Score	27.4 (28.13)	58.4 (19.79)	30.7 (24.56)	23.2 (19.85)	31.1 (24.32)
% Change from Baseline to Day **71**	-29.0 (36.38)	-13.2 (11.92)	-35.7 (37.54)	-52.0 (35.43)	-39.9 (36.13)
Absolute change from Baseline to Day **71**	-7.5 (17.71)	-8.5 (8.10)	-18.4 (23.12)	-25.2 (18.53)	-20.1 (20.14)

[0312]

[Table 25]

Day **85** BSA Score	25.1 (27.73)	58.0 (19.52)	30.7 (28.38)	23.6 (17.95)	30.7 (25.04)
% Change from Baseline to Day **85**	-33.4 (32.68)	-16.9 (16.63)	-37.8 (43.59)	-49.0 (37.34)	-40.4 (39.14)
Absolute change from Baseline to Day **85**	-8.4 (14.45)	-11.9 (11.45)	-20.6 (29.67)	-22.7 (15.74)	-20.5 (22.31)

[0313]
[Table 26]

Table 19: Summary of Percentage and Absolute Change in EASI Score from Baseline - all values represented as Mean (SD)

		mAb1			
	Placebo	**75mg**	**150mg**	**300mg**	**All Doses Combined**
No. Patients	16	8	22	21	51
Baseline EASI Score	22.8 (12.02)	36.9 (11.75)	30.0 (17.00)	27.4 (11.21)	30.0 (14.19)
Day **15** EASI Score	25.4 (20.13)	26.2 (7.72)	19.8 (15.05)	15.4 (8.57)	19.0 (12.06)
% Change from Baseline to Day **15**	8.7 (66.05)	-26.9 (19.29)	-31.1 (27.24)	-45.1 (19.90)	-36.3 (24.02)
Absolute change from Baseline to Day **15**	2.8 (14.11)	-10.7 (9.83)	-9.7 (12.02)	-12.0 (6.93)	-10.8 (9.67)
Day **29** EASI Score	17.2 (15.11)	17.7 (6.05)	13.1 (11.89)	11.3 (11.84)	13.1 (11.17)
% Change from Baseline to Day **29**	-25.4 (34.98)	-47.0 (21.93)	-55.0 (30.36)	-64.3 (25.83)	-57.7 (27.45)
Absolute change from Baseline to Day **29**	-3.6 (7.25)	-19.2 (15.11)	-16.6 (14.58)	-16.1 (7.69)	-16.8 (11.97)
Day **36** EASI Score	13.2 (11.97)	16.3 (7.74)	9.4 (10.27)	10.5 (8.69)	11.0 (9.42)
% Change from Baseline to Day **36**	-28.4 (41.10)	-51.5 (25.53)	-69.6 (22.46)	-61.9 (22.69)	-63.6 (23.41)
Absolute change from Baseline to Day **36**	-3.9 (7.94)	-21.5 (17.30)	-20.5 (14.98)	-16.1 (8.23)	-19.0 (13.13)
Day **43** EASI Score	12.9 97.13)	19.8 (10.41)	9.6 (11.01)	9.3 (8.29)	11.1 (10.32)
% Change from Baseline to Day **43**	-33.8 (28.94)	-39.4 (31.87)	-64.2 (33.89)	-66.4 (22.39)	-61.2 (29.98)
Absolute change from Baseline to Day **43**	-6.2 (4.71)	-17.0 (19.33)	-19.7 (16.63)	-16.8 (7.84)	-18.0 (13.76)
Day **57** EASI Score	13.0 (11.95)	27.0 (16.46)	12.2 (12.88)	10.4 (9.40)	13.5 (13.11)
% Change from Baseline to Day **57**	-28.7 (62.63)	-24.5 (47.21)	-57.3 (33.38)	-61.1 (24.91)	-54.3 (33.99)
Absolute change from Baseline to Day **57**	-5.4 (11.79)	-11.9 (22.95)	-18.4 (17.88)	-15.8 (9.69)	-16.5 (15.81)
Day **71** EASI Score	11.8 (9.22)	28.3 (13.06)	13.0 (10.86)	8.5 (9.21)	13.1 (12.06)
% Change from Baseline to Day **71**	-45.8 (31.06)	-14.5 (41.14)	-54.9 (32.01)	-71.3 (24.14)	-56.8 (34.68)
Absolute change from Baseline to Day **71**	-9.6 (8.23)	-9.4 (22.16)	-16.9 (15.41)	-19.1 (9.88)	-16.9 (14.32)

[0314]

[Table 27]

Day **85** EASI Score	9.8 (4.87)	27.1 (11.99)	14.2 (14.30)	10.5 (9.26)	14.0 (12.77)
% Change from Baseline to Day **85**	-44.8 (30.60)	-28.3 (29.69)	-51.3 (37.58)	-63.0 (25.55)	-53.9 (32.86)
Absolute change from Baseline to Day **85**	-9.3 (8.01)	-13.4 (18.94)	-16.6 (17.67)	-15.4 (7.57)	-15.7 (13.81)

[0315]

[Table 28]

Table 20: Summary of Percentage and Absolute Change in 5-D Pruritus Scale from Baseline - all values represented as Mean (SD)

	mAb1				
	Placebo	**75mg**	**150mg**	**300mg**	**All Doses Combined**
No. Patients	16	8	22	21	51
Baseline 5-D Pruritus Scale	16.9 (3.94)	21.5 (3.55)	19.0 (2.94)	18.7 (3.64)	19.3 (3.41)
Day **15** 5-D Pruritus Scale	15.0 (4.66)	14.0 (3.55)	14.0 (4.46)	12.5 (4.08)	13.4 (4.15)
% Change from Baseline to Day **15**	-5.6 (29.83)	-34.3 (15.43)	-26.6 (19.26)	-32.4 (17.60)	-30.3 (17.95)
Absolute change from Baseline to Day **15**	-1.4 (5.55)	-7.5 (3.82)	-5.0 (3.97)	-6.1 (3.93)	-5.9 (3.94)
Day **29** 5-D Pruritus Scale	14.8 93.77)	14.1 (3.31)	13.1 (5.03)	11.0 (4.86)	12.3 (4.79)
% Change from Baseline to Day **29**	-3.9 (20.07)	-33.0 (17.25)	-30.8 (23.71)	-40.8 (21.83)	-35.6 (22.02)
Absolute change from Baseline to Day **29**	-0.8 (3.41)	-7.4 (4.47)	-5.9 (4.84)	-7.7 (4.78)	-6.9 (4.73)
Day **43** 5-D Pruritus Scale	13.8 (3.71)	16.5 (4.54)	12.1 (4.64)	10.7 (4.83)	12.3 (5.04)
% Change from Baseline to Day **43**	-10.4 (31.60)	-21.4 (25.01)	-35.0 (22.07)	-40.8 (23.87)	-35.0 (23.86)
Absolute change from Baseline to Day **43**	-2.3 (5.25)	-5.0 (5.66)	-6.6 (4.45)	-7.6 (5.04)	-6.8 (4.90)
Day **57** 5-D Pruritus Scale	12.3 (3.35)	19.9 (3.98)	13.9 94.75)	11.6 (5.18)	14.0 (5.46)
% Change from Baseline to Day **57**	-19.0 (25.37)	-9.0 (20.15)	-27.2 (21.28)	-37.2 (21.68)	-28.1 (22.85)
Absolute change from Baseline to Day **57**	-3.4 (4.43)	-2.3 (4.46)	-5.1 (4.03)	-6.8 (4.61)	-5.3 (4.49)
Day **71** 5-D Pruritus Scale	13.5 (4.03)	19.4 (3.51)	15.3 (4.78)	12.9 (5.61)	14.7 (5.36)
% Change from Baseline to Day **71**	-11.6 (25.71)	-8.3 (14.91)	-18.9 (19.50)	-31.7 (24.53)	-23.3 (22.58)
Absolute change from Baseline to Day **71**	-2.0 (4.12)	-2.0 (3.39)	-3.4 (3.56)	-5.8 (4.70)	-4.3 (4.24)

[0316]

[Table 29]

Day **85** 5-D Pruritus Scale	14.1 (4.48)	18.6 (1.34)	15.2 (3.99)	14.6 (5.26)	15.3 (4.53)
% Change from Baseline to Day **85**	-5.4 (32.44)	-10.0 (22.58)	-18.5 (21.29)	-21.9 (23.41)	-19.0 (22.18)
Absolute change from Baseline to Day **85**	-1.2 (5.09)	-2.8 (4.92)	-3.7 (4.04)	-4.1 (4.52)	-3.7 (4.27)

[0317]

[Table 30]

Table 21: Summary of Percentage and Absolute Change in Average Weekly NRS Score from Baseline - all values represented as Mean (SD)

		mAb1			
	Placebo	**75mg**	**150mg**	**300mg**	**All Doses Combined**
No. Patients	10	8	22	21	51
Baseline NRS Score	5.8 (1.75)	7.0 (1.78)	6.0 (1.82)	5.7 (1.51)	6.0 (1.72)
Week **1** NRS Score	5.1 (1.73)	5.2 (2.50)	5.2 (1.91)	4.3 (1.52)	4.8 (1.88)
% Change from Baseline to Week **1**	-11.9 (23.13)	-27.3 (20.25)	-12.7 (18.26)	-21.6 (26.03)	-18.8 (22.42)
Absolute change from Baseline to Week **1**	-0.8 (1.40)	-1.7 (1.22)	-0.8 (1.30)	-1.4 (1.59)	-1.2 (1.44)
Week **2** NRS Score	4.7 (2.00)	4.0 (2.36)	4.5 (2.38)	3.7 (1.59)	4.1 (2.07)
% Change from Baseline to Week **2**	-14.8 (36.13)	-44.6 (21.90)	-26.9 (29.96)	-33.3 (26.69)	-32.4 (27.63)
Absolute change from Baseline to Week **2**	-1.0 (2.16)	-3.0 (1.350	-1.5 (1.76)	-2.0 (1.71)	-1.9 (1.73)
Week **3** NRS Score	5.0 (2.29)	3.9 (2.12)	4.0 (2.12)	3.3 (1.30)	3.7 (1.81)
% Change from Baseline to Week **3**	-10.2 (33.75)	-45.6 (21.67)	-35.4 (23.84)	-39.4 (25.92)	-38.8 (24.17)
Absolute change from Baseline to Week **3**	-0.7 (2.01)	-3.1 (1.30)	-2.0 (1.49)	-2.4 (1.65)	-2.3 (1.55)
Week **4** NRS Score	4.1 (2.03)	4.1 (1.95)	3.9 (2.38)	3.1 (1.84)	3.6 (2.10)
% Change from Baseline to Week **4**	-18.6 (40.12)	-42.3 (22.62)	-36.7 (29.33)	-45.4 (32.89)	-41.3 (29.63)
Absolute change from Baseline to Week **4**	-1.2 (2.29)	-2.9 (1.38)	-2.1 (1.85)	-2.6 (1.77)	-2.4 (1.74)
Week **5** NRS Score	4.2 (2.29)	4.1 (2.03)	3.5 (2.36)	3.0 (1.80)	3.4 (2.09)
% Change from Baseline to Week **5**	-18.9 (43.93)	-41.9 (24.53)	-43.4 (30.89)	-44.2 (32.74)	-43.5 (30.09)
Absolute change from Baseline to Week **5**	-1.2 (2.43)	-2.9 (1.55)	-2.5 (1.97)	-2.5 (1.92)	-2.6 (1.85)
Week **6** NRS Score	4.0 (2.40)	4.1 (2.22)	3.7 (2.38)	3.0 (1.84)	3.5 (2.14)
% Change from Baseline to Week **6**	-24.9 (42.63)	-42.7 (24.23)	-40.0 (30.52)	-46.9 (28.41)	-43.3 (28.31)
Absolute change from Baseline to Week **6**	-1.4 (2.36)	-2.8 (1.44)	-2.2 (1.86)	-2.6 (1.68)	-2.5 (1.71)
Week **7** NRS Score	3.4 (2.59)	4.4 (2.39)	3.7 (2.56)	2.8 (1.78)	3.4 (2.26)
% Change from Baseline to Week **7**	-35.5 (42.70)	-41.3 (21.96)	-40.3 (33.56)	-49.9 (30.73)	-44.5 (30.73)
Absolute change from Baseline to Week **7**	-1.9 (2.33)	-2.8 (1.10)	-2.2 (1.90)	-2.8 (1.83)	-2.5 (1.77)
Week **8** NRS Score	3.5 (2.61)	5.4 (2.40)	3.7 (2.24)	3.0 (1.98)	3.7 (2.24)
% Change from Baseline to Week **8**	-33.9 (38.63)	-27.8 (21.17)	-38.2 (33.09)	-45.6 (32.23)	-39.8 (31.29)
Absolute change from Baseline to Week **8**	-1.8 (2.19)	-1.9 (1.19)	-2.2 (1.80)	-2.6 (1.99)	-2.3 (1.80)

[0318]

[Table 31]

Week **9** NRS Score	3.6 (2.26)	5.5 (2.44)	4.1 (2.10)	3.0 (2.27)	3.9 (2.32)
% Change from Baseline to Week **9**	-32.8 (35.28)	-26.1 (17.08)	-31.5 (32.14)	-46.2 (36.56)	-36.9 (32.95)
Absolute change from Baseline to Week **9**	-1.7 (2.01)	-1.7 (1.02)	-1.8 (1.59)	-2.5 (2.10)	-2.1 (1.77)
Week **10** NRS Score	3.7 (2.51)	5.3 (2.33)	4.6 (2.18)	3.2 (1.99)	4.1 (2.21)
% Change from Baseline to Week **10**	-30.3 (41.78)	-21.7 (24.33)	-24.6 (28.77)	-43.4 (31.24)	-32.5 (30.36)
Absolute change from Baseline to Week **10**	-1.6 (2.31)	-1.4 (1.51)	-1.3 (1.37)	-2.4 (1.70)	-1.8 (1.59)
Week **11** NRS Score	2.8 (2.03)	5.8 (2.11)	5.0 (2.19)	3.2 (1.81)	4.4 (2.23)
% Change from Baseline to Week **11**	-40.2 (40.04)	-13.1 (26.33)	-14.2 (36.88)	-41.2 (31.87)	-25.1 (35.60)
Absolute change from Baseline to Week **11**	-2.0 (2.26)	-0.9 (1.61)	-0.8 (1.72)	-2.2 (1.64)	-1.4 (1.76)
Week **12** NRS Score	3.5 (1.48)	5.2 (2.37)	4.8 (2.47)	3.5 (2.37)	4.4 (2.44)
% Change from Baseline to Week **12**	-28.9 (29.54)	-25.4 (25.39)	-17.9 (33.42)	-35.5 (33.02)	-25.4 (32.53)
Absolute change from Baseline to Week **12**	-1.5 (1.66)	-1.7 (1.50)	-1.0 (1.77)	-1.7 (1.73)	-1.3 (1.71)

[0319]
[Table 32]

Table 22: Summary of Percentage and Absolute Change in IGA Score from Basel values represented as Mean (SD)

		mAb1			
	Placebo	**75mg**	**150mg**	**300mg**	**All Doses Combined**
No. Patients	16	8	22	21	51
Baseline IGA Score	3.6 (0.72)	4.1 (0.35)	3.9 (0.68)	3.5 (0.51)	3.8 (0.62)
Day **4** IGA Score	3.6 (0.73)	4.1 (0.35)	3.9 (0.71)	3.3 (0.48)	3.7 (0.65)
% Change from Baseline to Day **4**	-1.6 (6.25)	0.0 (0.00)	-1.1 (5.33)	-3.6 (8.96)	-2.0 (6.79)
Absolute change from Baseline to Day **4**	-0.1 (0.25)	0.0 (0.00)	0.0 (0.21)	-0.1 (0.36)	-0.1 (0.27)
Day **8** IGA Score	3.3 (0.90)	4.0 (0.00)	3.6 (0.85)	3.1 (0.54)	3.5 (0.73)
% Change from Baseline to Day **8**	-5.6 (21.28)	-2.5 (7.07)	-7.3 (12.55)	-10.3 (13.67)	-7.8 (12.46)
Absolute change from Baseline to Day **8**	-0.2 (0.68)	-0.1 (0.35)	-0.3 (0.46)	-0.4 (0.50)	-0.3 (0.46)
Day **15** IGA Score	3.4 (0.99)	3.6 (0.52)	3.0 (0.97)	2.9 (0.70)	3.1 (0.83)
% Change from Baseline to Day **15**	-2.8 (28.98)	-11.3 (16.20)	-23.7 (16.69)	-16.3 (18.16)	-18.5 (17.55)
Absolute change from Baseline to Day **15**	-0.1 (0.92)	-0.5 (0.76)	-0.9 (0.64)	-0.6 (0.60)	-0.7 (0.65)
Day **22** IGA Score	3.1 (0.67)	3.4 (0.52)	2.7 (0.73)	2.3 (0.80)	2.7 (0.80)
% Change from Baseline to Day **22**	-9.0 (19.61)	-17.5 (15.35)	-30.8 (12.76)	-32.5 (23.99)	-29.4 (19.17)
Absolute change from Baseline to Day **22**	-0.3 (0.65)	-0.8 (0.710	-1.2 (0.52)	-1.1 (0.79)	-1.1 (0.68)
Day **25** IGA Score	3.0 (0.89)	3.1 (0.35)	2.5 (0.87)	2.2 (0.89)	2.5 (0.86)
% Change from Baseline to Day **25**	-12.1 (29.43)	-23.8 (10.94)	-34.5 (18.64)	-35.7 (25.16)	-33.2 (21.05)
Absolute change from Baseline to Day **25**	-0.5 (0.93)	-1.0 (0.53)	-1.4 (0.790	-1.2 (0.83)	-1.2 (0.77)
Day **29** IGA Score	2.9 (1.08)	3.0 (0.53)	2.4 (0.99)	2.3 (0.85)	2.4 (0.89)
% Change from Baseline to Day **29**	-16.0 (24.48)	-26.3 (16.20)	-38.0 (24.02)	-34.9 (21.18)	-34.8 (21.68)
Absolute change from Baseline to Day **29**	-0.5 (0.80)	-1.1 (0.83)	-1.5 (1.00)	-1.2 (0.68)	-1.3 (0.85)

[0320]

[Table 33]

Day **36** IGA Score	2.9 (1.20)	3.0 (0.58)	2.2 (0.76)	2.4 (0.50)	2.4 (0.70)
% Change from Baseline to Day **36**	-16.7 (26.35)	-26.4 (17.49)	-44.1 (19.38)	-33.3 (9.13)	-37.1 (16.97)
Absolute change from Baseline to Day **36**	-0.5 (0.85)	-1.1 (0.90)	-1.7 (0.81)	-1.2 (0.40)	-1.4 (0.74)
Day **43** IGA Score	2.8 (1.06)	3.3 (0.76)	2.3 (1.02)	2.2 (0.83)	2.4 (0.97)
% Change from Baseline to Day **43**	-21.1 (26.91)	-19.3 (21.88)	-40.8 (28.04)	-39.0 (19.85)	-36.6 (24.53)
Absolute change from Baseline to Day **43**	-0.8 (0.97)	-0.9 (1.07)	-1.6 (1.04)	-1.3 (0.58)	1.4 (0.89)
Day **50** IGA Score	2.7 (1.19)	3.3 (0.82)	2.4 (1.07)	2.1 (0.80)	2.4 (1.00)
% Change from Baseline to Day **50**	-18.9 (30.98)	-18.3 (23.80)	-37. 2 (25.87)	-40.7 (21.93)	-36.0 (24.57)
Absolute change from Baseline to Day **50**	-0.6 (1.12)	-0.8 (1.17)	-1.5 (1.07)	-1.4 (0.70)	-1.3 (0.95)
Day **57** IGA Score	2.8 (1.20)	3.2 (0.75)	2.5 (1.03)	2.2 (0.97)	2.5 (1.00)
% Change from Baseline to Day **57**	-17.6 (33.45)	-22.5 (22.08)	-34.8 (25.21)	-36.3 (24.99)	-33.7 (24.60)
Absolute change from Baseline to Day **57**	-0.6 (1.01)	-1.0 (1.10)	-1.4 (1.07)	-1.2 (0.83)	-1.3 (0.97)
Day **64** IGA Score	2.7 (0.79)	3.5 (1.05)	2.7 (1.08)	2.1 (0.81)	2.6 (1.06)
% Change from Baseline to Day **64**	-18.9 (21.44)	-14.2 (29.23)	-30.9 (26.08)	-38.5 (20.61)	-31.5 (25.22)
Absolute change from Baseline to Day **64**	-0.6 (0.67)	-0.7 (1.37)	-1.2 (1.06)	-1.3 (0.70)	-1.2 (0.98)
Day **71** IGA Score	2.6 (0.81)	3.4 (0.89)	2.8 (0.86)	2.1 (1.15)	2.5 (1.10)
% Change from Baseline to Day **71**	-22.0 (20.84)	-17.0 (26.36)	-25.5 (27.32)	-41.7 (31.65)	-32.0 (30.18)
Absolute change from Baseline to Day **71**	-0.7 (0.65)	-0.8 (1.300	-1.1 (1.18)	-1.5 (1.10)	-1.2 (1.15)
Day **85** IGA Score	2.6 (1.17)	3.2 (0.84)	2.8 (0.99)	2.6 (0.96)	2.8 (0.96)
% Change from Baseline to Day **85**	-20.8 (36.69)	-22.0 (24.65)	-25.6 (31.31)	-24.6 (28.66)	-24.7 (28.77)
Absolute change from Baseline to Day **85**	-0.7 (1.16)	-1.0 (1.22)	-1.1 (1.23)	-0.8 (0.90)	-1.0 (1.07)

[0321]
[Table 34]

Table 23: Number (%) of subjects achieving EASI-50 at Day 29 and every study visit - LOCF

Number and % subjects with EASI50	Placebo (N=16)	75 mg (N=8)	150 mg (N=22)	300 mg (N=21)	All Doses Combined (N=51)
Week 4, Day 29	3 (18.8%)	3 (37.5%)	12 (54.5%)	15 (71.4%)	30 (58.8%)
Week 2, Day 15	0	0	6 (27.3%)	11 (52.4%)	17 (33.3%)
Week 5, Day 36	3 (18.8%)	5 (62.5%)	16 (72.7%)	15 (71.4%)	36 (70.6%)
Week 6, Day 43	3 (18.8%)	2 (25.0%)	14 (63.6%)	16 (76.2%)	32 (62.7%)
Week 8, Day 57	5 (31.3%)	2 (25.0%)	12 (54.5%)	13 (61.9%)	27 (52.9%)
Week 10, Day 71	6 (37.5%)	1 (12.5%)	13 (59.1%)	16 (76.2%)	30 (58.8%)
Week 12, Day 85	3 (18.8%)	1 (12.5%)	12 (54.5%)	17 (81.0%)	30 (58.8%)

[0322]
[Table 35]

Table 24: Number (%) of subjects achieving EASI-25 at Day 29 and every study visit - LOCF

Number and % subjects with EASI25	Placebo (N=16)	75 mg (N=8)	150 mg (N=22)	300 mg (N=21)	All Doses Combined (N=51)
Week 4, Day 29	4 (25.0%)	7 (87.5%)	16 (72.7%)	18 (85.7%)	41 (80.4%)
Week 2, Day 15	3 (18.8%)	5 (62.5%)	13 (59.1%)	16 (76.2%)	34 (66.7%)
Week 5, Day 36	6 (37.5%)	7 (87.5%)	19 (86.4%)	18 (85.7%)	44 (86.3%)
Week 6, Day 43	7 (43.8%)	5 (62.5%)	19 (86.4%)	18 (85.7%)	42 (82.4%)
Week 8, Day 57	8 (50.0%)	4 (40.0%)	16 (72.7%)	17 (81.0%)	37 (72.5%)
Week 10, Day 71	8 (50.0%)	3 (37.5%)	17 (77.3%)	19 (90.5%)	39 (76.5%)
Week 12, Day 85	9 (56.3%)	3 (37.5%)	16 (72.7%)	20 (95.2%)	39 (76.5%)

[0323]
[Tale 36]

Table 25: Number (%) of subjects achieving EASI-75 at Day 29 and every study visit - LOCF

Number and % subjects with EASI75	Placebo (N=16)	75 mg (N=8)	150 mg (N=22)	300 mg (N=21)	All Doses Combined (N=51)
Week 4, Day 29	1 (6.3%)	1 (12.5%)	6 (27.3%)	8 (38.1%)	15 (29.4%)
Week 2, Day 15	0	0	1 (4.5%)	1 (4.8%)	2 (3.9%)
Week 5, Day 36	1 (6.3%)	1 (12.5%)	9 (40.9%)	7 (33.3%)	17 (33.3%)
Week 6, Day 43	1 (6.3%)	1 (12.5%)	8 (36.4%)	6 (28.6%)	15 (29.4%)
Week 8, Day 57	2 (12.5%)	1 (12.5%)	9 (40.9%)	6 (28.6%)	16 (31.4%)
Week 10, Day 71	2 (12.5%)	1 (12.5%)	6 (27.3%)	11 (52.4%)	18 (35.5%)
Week 12, Day 85	2 (12.5%)	1 (12.5%)	6 (27.3%)	7 (33.3%)	14 (27.5%)

[0324]

mAb1 was well-tolerated and effective in adults with moderate-to-severe AD. mAb1 administration significantly improved AD disease activity and severity. At 4 weeks, 150 mg and 300 mg mAb1 achieved significant improvements vs. placebo for change from baseline in %BSA ($p < 0.05$) (Figure 15), IGA ($p < 0.001$) (Figure 16), EASI ($p < 0.001$) (Figure 17), and pruritus NRS ($p < 0.01$, 300 mg) (Figure 18). More patients had ≥ 50% reduction in EASI score with 150 mg mAb1 (54.5%) and with 300 mg (71.4%) vs. placebo (18.8%; $p < 0.05$ for both) (Figures 19 and 20). More patients achieved EASI-25, EASI-50, and EASI-75 with mAb1 over placebo at week 4 (Figure 21).

[0325]

For 300 mg mAb1, significant improvement was seen within 2 weeks in %BSA ($p < 0.02$), IGA ($p < 0.05$), and EASI ($p < 0.0001$). Improvements for BSA, IGA and EASI ($p < 0.05$ vs. placebo) were maintained for 8 weeks. The proportion of patients with IGA 0 or 1 at week 4 was higher than placebo, but not statistically significant (Figure 22).

[0326]

The most common treatment-emergent adverse events (AEs) with mAb1 administration were nasopharyngitis (19.6% vs. 12.5% for placebo) and headache (11.8% vs. 6.3% for placebo).

[0352]

[Example 10]

Repeat-dose Clinical Trial of Subcutaneously Administered anti-IL-4R Antibody (mAb1) in adult patients with moderate-to-severe atopic dermatitis

A. Study Design

This study was a 28-week randomized, double-blind, placebo-controlled study of the anti-IL-4R mAb, referred herein as "mAb1", administered subcutaneously in patients with moderate-to-severe atopic dermatitis. The treatment period was 12 weeks in duration with the patients followed for a further 16 weeks after end of the treatment. [0353]

109 patients were included and randomized in the ratio of 1:1 for the study (54 in placebo and 55 for 300 mg of the antibody). 43 patients (30 in placebo and 13 in 300 mg group) withdrew from the study. Randomization was stratified according to IgE levels (IgE < 150 kU/L vs. ≥ 150 kU/L at the screening visit) to test the efficacy of mAb1 in patients with extrinsic or intrinsic form of AD. Patients who met eligibility criteria underwent day 1/baseline assessments, randomization, and then received 300 mg of mAb1 or placebo SC. Each weekly dose of study drug was given as one 2-mL injection, or was split into two 1-mL injections. Patients returned for weekly clinic visits and received an injection of study drug on days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78. Patients were closely monitored at the study site for a minimum of 2 hours after each dose of study drug. The end of the treatment period was day 85. Follow-up visits occurred on days 92, 99, 106, 113, 120, 127, 134, 141, 148, 155, 162, 169, 176, 183, 190, and the end of study visit on day 197.

[0354]

Inclusion criteria for the study were as follows: (1) Male or female 18 years or older; (2) Chronic AD, diagnosed by the Eichenfield revised criteria of Hannifin and Rajka, that has been present for at least 3 years before the screening visit; (3) EASI score ≥ 16 at the screening and baseline visits; (4) IGA score ≥ 3 at the screening and baseline visits; (5) ≥ 10% BSA of AD involvement at the screening and baseline visits; (6) history of inadequate response to a stable (≥ 1 month) regimen of topical corticosteroids or calcineurin inhibitors as treatment for AD within the last 3 months before the screening visit; (7) Patients must have applied a stable dose of an additive-free, basic bland emollient twice-daily for at least 7 days before the baseline visit; and (8) Willingness, commitment, and ability to return for all clinic visits and complete all study-related procedures and willing and able to sign the informed consent form (ICF). [0355]

Exclusion criteria for the study were as follows: (1) Prior treatment with mAb1; (2) Presence of any of the following laboratory abnormalities at the screening visit: white blood cell count < 3.5×10^3/μI_; platelet count < 125×10^3/μI_; neutrophil count < 1.75×10^3/μI_; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 1.5× the

ULN; and CPK > 2× the ULN; (3) Positive or indeterminate results at the screening visit for hepatitis B surface antigen, hepatitis B core antibody or hepatitis C antibody; (4) Onset of a new exercise routine or major change to a previous exercise routine within 4 weeks prior to screening (visit 1). Subjects had to be willing to maintain a similar level of exercise for the duration of the study and to refrain from unusually strenuous exercise for the duration of the trial; (5) Treatment with an investigational drug within 8 weeks or within 5 half-lives, if known, whichever is longer, before the baseline visit; (6) Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit; (7) Treatment with allergen immunotherapy within 6 months before the baseline visit; (8) Treatment with leukotriene inhibitors within 4 weeks before the baseline visit; (9) Treatment with systemic corticosteroids within 4 weeks before the baseline visit; (10) Treatment with topical corticosteroids, tacrolimus, and/or pimecrolimus within 1 week before the baseline visit; (11) Systemic treatment for AD with an immunosuppressive/immunomodulating substance, eg. Cyclosporine, mycophenolate-mofetil, IFN-γ, phototherapy, (narrow band uvB, uvB, uvA1, psoralen + uvA), azathioprine, methotrexate, or biologics, within 4 weeks before the baseline visit; (12) three or more bleach baths during any week within the 4 weeks before the baseline visit; (13) Treatment of AD with a medical device (e.g. Atopiclair®, MimyX®, Epicerum®, Cerave®, etc) within 1 week before the baseline visit; (14) Chronic or acute infection requiring treatment with oral or IV antibiotics, antivirals, anti-parasitics, anti-protozoals, or anti-fungals within 4 weeks before the screening visit, or superficial skin infections within 1 week before the screening visit; (15) Known history of HIV infection; (16) History of hypersensitivity reaction to doxycycline or related compounds; (17) History of clinical parasite infection, other than vaginal trichomoniasis; (18) History of malignancy within 5 years before the baseline visit, with the following exceptions; patients with a history of completely treated carcinoma in situ of cervix, and non-metastatic squamous or basal cell carcinoma of the skin are allowed; (19) Planned surgical procedure during the length of the patient's participation in the study; (20) Use of a tanning booth/parlor within 4 weeks before the screening visit; (21) Significant concomitant illness or history of significant illness such as psychiatric, cardiac, renal, neurological, endocrinological, metabolic or lymphatic disease, or any other illness or condition that would have adversely affected the subject's participation in this study; (22) Pregnant or breast-feeding women; and/or (23) Unwilling to use adequate birth control. Adequate birth control is defined as agreement to consistently practice an effective and accepted method of contraception throughout the duration of the study and for 16 weeks after last dose of study drug. For females, adequate birth

control methods are defined as: hormonal contraceptives, intrauterine device (IUD), or double barrier contraception (ie, condom + diaphragm, condom or diaphragm + spermicidal gel or foam). For males, adequate birth control methods are defined as: double barrier contraception (ie, condom + diaphragm, condom or diaphragm + spermicidal gel or foam). For females, menopause is defined as 24 months without menses; if in question, a follicle-stimulating hormone of ≥ 25 U/mL must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable.

[0356]

B. Efficacy Variables

The primary endpoint was the percent change in EASI score from baseline to week 12. The secondary endpoints measured in this study included: (1) proportion of patients who achieved an investigator's global assessment (IGA) score of 0 or 1 at week 12; (2) proportion of patients who achieved ≥ 50% overall improvement in EASI score (also called EASI 50) from baseline to week 12; (3) change in EASI score from baseline to week 12; (4) change and percent change in IGA score, body surface area involvement of atopic dermatitis (BSA), eczema area and severity index (EASI), SCORAD, Pruritus NRS and 5-D pruritus scale from baseline to week 12; (5) Incidence of TEAEs from baseline through week 28; (6) change from baseline in eosinophils, TARC, Phadiatop™ results, and total IgE associated with response; (7) change in QoLIAD from baseline to week 12; (8) proportion of patients who achieve reduction of IGA score of ≥ 2 from baseline to week 12; (9) proportion of patients who achieve reduction of IGA score of ≥ 3 from baseline to week 12; and (10) PD response of circulating eosinophils, TARC and total IgE.

[0357]

Baseline for efficacy variable is defined as the last non-missing value on or before the date of randomization. For the patient who has no value on or before his/her randomization date the last non-missing value on or before the date of first dose injection will be used as baseline.

[0358]

Investigation Procedures

The efficacy variables IGA, BSA, EASI, SCORAD, 5-D Pruritus scale, and Pruritus NRS rating have been described elsewhere herein (see, e.g., Example 7).

[0359]

The IGA, BSA, EASI and SCORAD scores were assessed at every clinic visit. Patients underwent 5-D pruritus assessment at the following visits: screening, day

1/baseline (pre-dose), and days 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183 and 197 (end of study) or early termination. Patients used the IVRS to record their Pruritus NRS score twice daily through the last study visit.

[0360]

Quality of Life Index for Atopic Dermatitis (QoLIAD): The QoLIAD is a 25-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on QoL. The format is a simple yes/no response to 25 items with a scoring system of 0 to 25; a high score is indicative of a poor QoL. The questionnaire was administered at screening and day 1/baseline (pre-dose), and days 29, 57, 85, 99, 113, 127, 141, 155, 169, 183, and 197 (end of study) or early termination.

[0361]

C. Investigational Treatment

mAb1 drug product was supplied as a lyophilized powder in a 5 ml glass vial for SC administration. When delivered SC, the mAb1 drug product was reconstituted with 2.5 ml of sterile water for injection, yielding a solution containing 150 mg/mL of mAb1. The dose level of mAb1 tested was 300 mg for SC administration. mAb1 or placebo was administered as 1 (2 mL) or 2 (1 mL) SC injections in the clinic on day 1/baseline and days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78. Although it was preferred that each weekly dose of study drug be given as one 2-mL injection, each weekly dose could be split into two 1-mL injections. Subcutaneous injection sites were alternated between the following sites: back of arms, abdomen (except the navel or waist area), and upper thighs. Administration to the extremities was not allowed due to the possibility of different absorption and bioavailability. If administration of multiple injections were required on the same day, each injection was delivered at a different injection site (e.g., 1 injection administered in the right lower quadrant of the abdomen and the other in the left lower quadrant of the abdomen). Subcutaneous injection sites were alternated so that the same sites were not injected for 2 consecutive weeks.

[0362]

Placebo matching mAb1 was prepared in the same formulation as mAb1, but without addition of antibody.

[0363]

Patients were monitored at the study site for a minimum of 2 hours after each dose of study drug.

[0364]

In addition, patients were required to apply stable doses of an additive-free, basic

bland emollient twice daily for at least 7 days before the baseline visit and throughout study participation. Patients reported compliance with background treatment during the study using the IVRS or IWRS. The system prompted patients to answer the following question about emollient use: "Did you use a moisturizer approved by the study doctor on the affected areas of your skin?"

[0365]

D. Safety Assessment

Safety was assessed throughout the study by monitoring Adverse Events and Serious Adverse Events.

[0366]

An Adverse Event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE can, therefore, be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal (investigational) product. AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug; abnormal laboratory findings considered by the Investigator to be clinically significant; and any untoward medical occurrence.

[0367]

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose results in death; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/ incapacity; is a congenital anomaly/ birth defect; or is an important medical event.

[0368]

In addition, laboratory safety variables, vital sign variables, 12-lead electrocardiography (ECG) variables, and physical examination variables were measured throughout the study.

[0369]

The clinical laboratory data consists of hematology, blood chemistry and urinalysis. Blood samples for hematology testing were collected at every study visit; blood samples for serum chemistry testing and urine samples for urinalysis were collected to measure overall patient health at screening, day 1/ baseline (pre-dose), day 15, day 29, day 43, day 57, day 71, day 85, day 99, day 113, day 141, day 169, and day 197 (end-of study) or early termination if subject is discontinued from the study.

[0370]

Vital sign parameters include respiratory rate (bpm), pulse rate (bpm), systolic and diastolic blood pressure (mmHg) and body temperature (°C). Vital signs were collected (pre-dose, on dosing days) at screening and day 1/baseline, and days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 99, 113, 141, 169 and 197 (end of study) or early termination. Vital signs were taken at 1 and 2 hours post-injection following the study drug dose on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78.

[0371]

12-Lead ECG parameters include: Ventricular HR, PR interval, QRS interval, corrected QT interval (QTcF = QT/[$RR^{0.33}$] and QTcB = QT/[$RR^{0.5}$]) ECG status: normal, abnormal not clinical significant or abnormal clinical significant. A standard 12-lead ECG was performed at screening, day 141, and day 197 (end of study) or early termination.

[0372]

Research samples (serum/RNA/plasma) were collected at screening and day 1 /baseline (pre-dose), and days 8, 15, 22, 29, 57, 85, and 197 (end of study) or early termination, and at unscheduled visits.

[0373]

A thorough and complete physical examination was performed at screening, day 85, and day 197 (end of study) or early termination.

[0374]

E. Data Analysis

1. Analyses of Exploratory Efficacy Variables

All categorical variables were analyzed using the Fisher's Exact test with nominal p-value and confidence intervals reported. All continuous variables were analyzed by the ANalysis of COVAriance (ANCOVA) using baseline IgE stratum (< 150 kU/L vs. ≥ 150 kU/L at the screening visit). Unless otherwise specified, assessments of changes from baseline and construction of confidence intervals for continuous measures were based on an ANCOVA model which includes treatment as the main factor and baseline value as covariates. Point estimate and 95% CI of the difference in adjusted mean change from baseline between two treatment groups are provided. Missing values will be imputed by the last observation carried forward (LOCF) approach. In the event that the model assumptions are not warranted, the Rank-based analysis of covariates will be used.

[0375]

2. Analysis of Safety Data

The safety analysis is based on the reported AEs, clinical laboratory evaluations,

vital signs, and 12-lead ECG. Thresholds for Potentially Clinically Significant Values (PCSV) in laboratory variables, vital signs and ECG are defined in SAP. The time interval to detect any event or abnormality is between the infusion of study medication and end of study. Data collected outside this interval are excluded from the calculation of descriptive statistics and identification of abnormalities for laboratory evaluations, vital signs and ECG.

[0376]

F. Safety: Results

mAb1 was generally well-tolerated with a favorable safety profile. The overall adverse event (AE) profile was characteristic of a healthy population. No deaths were reported. There were 8 patients with SAEs, of which 1 was in mAb1 group (facial bones fracture) and 7 were in the placebo group (angina pectoris, cellulitis, eczema herpeticum, skin bacterial infection, renal failure, asthmatic crisis, lung disorder and atopic dermatitis). There were 8 patients with TEAE resulting in discontinuation from study drug, of which 1 was in the mAb1 group and 7 in the placebo group. There were 87 patients with at least one TEAE (n = 43 [78.2%] in mAb1 vs. 44 [81.5%] in placebo group). The most frequent TEAEs were nasopharyngitis infections in subjects dosed with mAb1 (n = 22 [40%] vs. 10 [18.5%] for placebo). Other TEAEs in the treatment group included eye infections, nervous system disorders, and general disorders and administration site conditions. No other clinically significant laboratory test results (blood chemistry, hematology, or urinalysis) were reported during the study. No trends were seen in mean/median baseline in any laboratory parameter. There were no significant trends in mean or median changes from baseline in temperature or pulse throughout the study. No clinically significant abnormalities were seen on physical examination results, ECGs or vital signs.

[0377]

Subcutaneous administration of mAb1 to adult patients with moderate-to-severe AD was generally safe and well-tolerated.

[0378]

G. Efficacy: Results

The baseline and exploratory efficacy results obtained from the study are summarized in Figures 23 - 33 and Tables 27 - 35. As noted above, patients were treated with 300 mg subcutaneous mAb1 once a week for 12 weeks, or with placebo.

[0379]
[Table 38]

Table 27: Summary of Baseline Characteristics - all values represented as Mean (SD)

	Placebo	mAb1 300 mg	All Subjects Combined
No. Patients	54	55	109
Age (years) Mean (SD)	39.4 (12.29)	33.7 (10.41)	36.5 (11.69)
Ethnicity n (%)			
Hispanic or Latino	1 (1.9%)	3 (5.5%)	4 (3.7%)
Not Hispanic or Latino	53 (98.1%)	52 (94.5%)	105 (96.3%)
Gender n (%)			
Male	27 (50.0%)	31 (56.4%)	58 (53.2%)
Female	27 (50.0%)	24 (43.6%)	51 (46.8%)
Height (cm) Mean (SD)	171.2 (9.89)	173.4 (9.88)	172.3 (9.90)
Weight (kg) Mean (SD)	72.41 (17.539)	78.13 (17.416)	75.30 (17.632)
BMI (kg/m^2) Mean (SD)	24.51 (4.639)	25.89 (4.837)	25.20 (4.768)
Chronic Atopic Dermatitis Diagnosis Age	14.4 (18.35)	6.6 (10.53)	10.5 (15.37)
BSA	50.8 (24.14)	46.8 (24.55)	48.8 (24.32)
EASI Score	30.8 (13.63)	28.4 (13.57)	29.6 (13.59)
IGA Score	4.0 (0.69)	3.9 (0.67)	3.9 (0.68)
NRS Score	5.8 (1.93)	6.1 (1.34)	5.9 (1.66)
SCORAD Score	69.1 (13.38)	66.7 (13.82)	67.9 (13.59)
Pruritus 5-D Scale	18.7 (3.50)	18.4 (3.04)	18.5 (3.26)

[0380]
[Table 39]

Table 28: Summary of Percentage and Absolute Change in EASI Score from Baseline to Week 12 and Each Visit during Follow-up period - all values represented as Mean (SD)

	Placebo	300mg mAb1
No. Patients	54	55
Baseline EASI Score	30.8 (13.63)	28.4 (13.57)
Day **85** EASI Score	24.4 (19.01)	8.5 (12.15)
% Change from Baseline to Day **85**	-23.3 (49.26)	-74.0 (26.94)
Absolute change from Baseline to Day **85**	-6.4 (14.85)	-19.9 (11.52)
Day **99** EASI Score	24.2 (19.15)	8.4 (11.86)
% Change from Baseline to Day **99**	-23.2 (49.42)	-73.5 (27.21)
Absolute change from Baseline to Day **99**	-6.6 (15.20)	-20.0 (12.24)
Day **113** EASI Score	24.1 (18.80)	9.1 (12.13)
% Change from Baseline to Day **113**	-23.4 (47.75)	-71.4 (27.03)
Absolute change from Baseline to Day **113**	-6.7 (14.96)	-19.4 (11.42)
Day **127** EASI Score	24.5 (18.91)	9.2 (12.41)
% Change from Baseline to Day **127**	-22.1 (47.11)	-71.2 (27.39)
Absolute change from Baseline to Day **127**	-6.3 (14.98)	-19.2 (11.15)
Day **141** EASI Score	23.8 (18.47)	9.4 (12.18)
% Change from Baseline to Day **141**	-23.9 (47.01)	-70.8 (26.91)
Absolute change from Baseline to Day **141**	-7.0 (14.77)	-19.0 (10.86)
Day **155** EASI Score	24.0 (18.27)	9.9 (12.40)
% Change from Baseline to Day **155**	-23.0 (46.22)	-68.8 (27.35)
Absolute change from Baseline to Day **155**	-6.7 (14.49)	-18.5 (10.74)
Day **169** EASI Score	23.5 (18.22)	11.0 (12.76)
% Change from Baseline to Day **169**	-24.2 (46.66)	-64.4 (29.19)
Absolute change from Baseline to Day **169**	-7.3 (14.93)	-17.5 (10.82)
Day **183** EASI Score	23.5 (18.57)	10.8 (13.00)
% Change from Baseline to Day **183**	-24.6 (47.35)	-65.0 (29.21)
Absolute change from Baseline to Day **183**	-7.3 (15.12)	-17.6 (10.93)
Day **197** EASI Score	23.4 (18.59)	11.0 (13.13)
% Change from Baseline to Day **197**	-25.0 (48.57)	-64.0 (30.80)
Absolute change from Baseline to Day **197**	-7.4 (15.23)	-17.4 (11.88)

[0381]
[Table 40]

Table 29: Summary of Percentage and Absolute Change in IGA Score from Baseline to Week 12 and Each Visit during Follow-up period - all values represented as Mean (SD)

	Placebo	300mg mAb1
No. Patients	54	55
Baseline IGA Score	4.0 (0.69)	3.9 (0.67)
Day **85** IGA Score	3.4 (1.19)	2.0 (1.15)
% Change from Baseline to Day **85**	-14.7 (27.37)	-49.5 (25.94)
Absolute change from Baseline to Day **85**	-0.6 (1.07)	-1.9 (0.98)
Day **99** IGA Score	3.4 (1.16)	2.1 (1.17)
% Change from Baseline to Day **99**	-14.0 (27.03)	-45.8(26.98)
Absolute change from Baseline to Day **99**	-0.6 (1.06)	-1.7 (1.06)
Day **113** IGA Score	3.3 (1.20)	2.2 (1.08)
% Change from Baseline to Day **113**	-15.9 (27.82)	-43.1 (25.53)
Absolute change from Baseline to Day **113**	-0.6 (1.12)	-1.7 (1.06)
Day **127** IGA Score	3.4 (1.16)	2.2 (1.16)
% Change from Baseline to Day **127**	-14.5 (26.66)	-44.1 (27.06)
Absolute change from Baseline to Day **127**	-0.6 (1.07)	-1.7 (1.07)
Day **141** IGA Score	3.4 (1.15)	2.2 (1.12)
% Change from Baseline to Day **141**	-15.0 (26.52)	-42.8 (26.01)
Absolute change from Baseline to Day **141**	-0.6 (1.05)	-1.6 (1.01)
Day **155** IGA Score	3.4 (1.14)	2.3 (1.08)
% Change from Baseline to Day **155**	-14.2 (25.89)	-41.5 (25.20)
Absolute change from Baseline to Day **155**	-0.6 (1.02)	-1.6 (1.01)
Day **169** IGA Score	3.3 (1.17)	2.5 (1.07)
% Change from Baseline to Day **169**	-15.9 (26.96)	-36.0 (25.87)
Absolute change from Baseline to Day **169**	-0.6 (1.08)	-1.4 (1.03)
Day **183** IGA Score	3.3 (1.18)	2.4 (1.10)
% Change from Baseline to Day **183**	-16.3 (27.33)	-37.2 (26.93)
Absolute change from Baseline to Day **183**	-0.7 (1.10)	-1.5 (1.09)
Day **197** IGA Score	3.3 (1.29)	2.3 (1.09)
% Change from Baseline to Day **197**	-16.5 (30.18)	-39.0 (27.42)
Absolute change from Baseline to Day **197**	-0.7 (1.20)	-1.5 (1.10)

[0382]
[Table 41]

Table 30: Summary of Absolute Change in BSA Score from Baseline to Week 12 and Each Visit during Follow-up period - all values represented as Mean (SD)

	Placebo	**300mg mAb1**
No. Patients	54	55
Baseline BSA Score	50.8 (24.13)	46.8 (24.55)
Day **85** BSA Score	41.8 (30.44)	19.4 (23.43)
Absolute change from Baseline to Day **85**	-9.0 (21.07)	-27.4 (22.81)
Day **99** BSA Score	41.7 (30.85)	19.9 (22.85)
Absolute change from Baseline to Day **99**	-9.2 (21.85)	-26.9 (22.74)
Day **113** BSA Score	41.3 (30.52)	20.8 (23.16)
Absolute change from Baseline to Day **113**	-9.5 (21.34)	-26.0 (21.90)
Day **127** BSA Score	42.1 (30.41)	21.4 (23.48)
Absolute change from Baseline to Day **127**	-8.7 (20.72)	-25.4 (21.29)
Day **141** BSA Score	41.5 (29.85)	21.3 (22.88)
Absolute change from Baseline to Day **141**	-9.4 (20.57)	-25.5 (21.50)
Day **155** BSA Score	41.5 (29.61)	22.1 (23.05)
Absolute change from Baseline to Day **155**	-9.3 (20.26)	-24.6 (21.55)
Day **169** BSA Score	41.2 (29.28)	24.6 (24.15)
Absolute change from Baseline to Day **169**	-9.6 (20.35)	-22.2 (21.50)
Day **183** BSA Score	41.0 (30.28)	24.1 (24.15)
Absolute change from Baseline to Day **183**	-9.9 (21.35)	-22.7 (22.86)
Day **197** BSA Score	40.5 (29.95)	24.9 (25.70)
Absolute change from Baseline to Day **197**	-10.4 (21.40)	-21.9 (24.11)

[0383]
[Table 42]

Table 31: Summary of Absolute Change in SCORAD Score from Baseline to Week 12 and Each Visit during Follow-up period - all values represented as Mean (SD)

	Placebo	**300mg mAb1**
No. Patients	54	55
Baseline SCORAD Score	69.1 (13.38)	66.7 (13.82)
Day **85** SCORAD Score	59.3 (23.44)	31.7 (22.08)
Absolute change from Baseline to Day **85**	-9.8 (20.53)	-35.0 (19.43)
Day **99** SCORAD Score	58.8 (23.35)	32.5 (20.99)
Absolute change from Baseline to Day **99**	-10.3 (21.33)	-34.3 (18.94)
Day **113** SCORAD Score	59.1 (22.30)	34.0 (2051)
Absolute change from Baseline to Day **113**	-10.0 (20.89)	-32.7 (18.48)
Day **127** SCORAD Score	59.9 (22.36)	34.0 (21.25)
Absolute change from Baseline to Day **127**	09.2 (20.59)	-32.7 (18.23)
Day **141** SCORAD Score	59.0 (21.85)	33.9 (20.51)
Absolute change from Baseline to Day **141**	-10.1 (20.12)	-32.8 (17.97)
Day **155** SCORAD Score	59.0 (22.50)	35.1 (20.16)
Absolute change from Baseline to Day **155**	-10.0 (20.17)	-31.6 (17.99)
Day **169** SCORAD Score	58.5 (22.33)	37.1 (20.82)
Absolute change from Baseline to Day **169**	-10.6 (20.90)	-29.6 (19.15)
Day **183** SCORAD Score	58.7 (22.47)	37.5 (20.89)
Absolute change from Baseline to Day **183**	-10.4 (20.86)	-29.2 (19.50)
Day **197** SCORAD Score	57.8 (23.82)	38.8 (22.04)
Absolute change from Baseline to Day **197**	-11.3 (22.05)	-27.9 (21.70)

[0384]
[Table 43]

Table 32: Summary of Absolute Change in 5-D Pruritus Scale from Baseline to Week 12 and Each Week during Follow-up period - all values represented as Mean (SD)

	Placebo	**300mg mAb1**
No. Patients	54	55
Baseline 5-D Pruritus Score	18.7 (3.50)	18.4 (3.04)
Day **85** 5-D Pruritus Score	16.9 (5.33)	11.0 (4.22)
Absolute change from Baseline to Day **85**	-1.9 (4.28)	-7.4 (4.33)
Day **99** 5-D Pruritus Score	16.7 (5.28)	11.3 (3.96)
Absolute change from Baseline to Day **99**	-2.0 (4.63)	-7.0 (4.41)
Day **113** 5-D Pruritus Score	16.5 (5.57)	11.7 (4.05)
Absolute change from Baseline to Day **113**	-2.2 (4.91)	-6.7 (4.21)
Day **127** 5-D Pruritus Score	16.7 (5.44)	11.5 (4.07)
Absolute change from Baseline to Day **127**	-2.0 (4.72)	-6.9 (4.24)
Day **141** 5-D Pruritus Score	16.4 (5.67)	11.8 (4.19)
Absolute change from Baseline to Day **141**	-2.3 (5.12)	-6.6 (4.56)
Day **155** 5-D Pruritus Score	16.6 (5.53)	12.0 (4.21)
Absolute change from Baseline to Day **155**	-2.1 (4.90)	-6.4 (4.49)
Day **169** 5-D Pruritus Score	16.8 (5.35)	12.7 (4.20)
Absolute change from Baseline to Day **169**	-1.9 (4.78)	-5.7 (4.58)
Day **183** 5-D Pruritus Score	16.6 (5.59)	12.8 (4.56)
Absolute change from Baseline to Day **183**	-2.1 (5.02)	-5.6 (4.90)
Day **197** 5-D Pruritus Score	16.6 (5.50)	13.1 (4.85)
Absolute change from Baseline to Day **197**	-2.1 (5.12)	-5.3 (5.06)

[0385]
[Table 44]

Table 33: Summary of Absolute Change in Average NRS Score from Baseline to Week 12 and Each Week during Follow-up period - all values represented as Mean (SD)

	Placebo	**300mg mAb1**
No. Patients	54	55
Baseline NRS Score	5.8 (1.93)	6.1 (1.34)
Day **85** NRS Score	4.9 (2.53)	2.6 (1.67)
Absolute change from Baseline to Day **85**	-0.9 (2.07)	-3.5 (2.00)
Day **92** NRS Score	4.8 (2.57)	2.8 (1.68)
Absolute change from Baseline to Day **92**	-1.0 (2.07)	-3.4 (2.12)
Day **99** NRS Score	4.7 (2.54)	2.7 (1.72)
Absolute change from Baseline to Day **99**	-1.0 (2.06)	-3.4 (2.17)
Day **106** NRS Score	4.8 (2.59)	2.7 (1.63)
Absolute change from Baseline to Day **106**	-1.0 (2.15)	-3.4 (2.08)
Day **113** NRS Score	4.9 (2.69)	2.7 (1.63)
Absolute change from Baseline to Day **113**	-0.9 (2.21)	-3.4 (2.00)
Day **120** NRS Score	4.8 (2.61)	2.7 (1.68)
Absolute change from Baseline to Day **120**	-1.0 (2.18)	-3.4 (2.07)
Day **127** NRS Score	4.8 (2.68)	2.8 (1.79)
Absolute change from Baseline to Day **127**	-1.0 (2.24)	-3.3 (2.20)
Day **134** NRS Score	4.7 (2.75)	2.8 (1.78)
Absolute change from Baseline to Day **134**	-1.1 (2.24)	-3.3 (2.18)
Day **141** NRS Score	4.7 (2.73)	2.9 (1.89)
Absolute change from Baseline to Day **141**	-1.1 (2.26)	-3.2 (2.28)
Day **148** NRS Score	4.7 (2.75)	2.9 (1.89)
Absolute change from Baseline to Day **148**	-1.1 (2.28)	-3.2 (2.28)
Day **155** NRS Score	4.7 (2.75)	2.9 (1.86)
Absolute change from Baseline to Day **155**	-1.1 (2.30)	-3.2 (2.19)
Day **162** NRS Score	4.7 (2.75)	3.0 (1.93)
Absolute change from Baseline to Day **162**	-1.1 (2.29)	-3.1 (2.28)
Day **169** NRS Score	4.7 (2.75)	3.2 (1.99)
Absolute change from Baseline to Day **169**	-1.1 (2.28)	-3.0 (2.43)

[0386]
[Table 45]

Day **176** NRS Score	4.7 (2.74)	3.2 (2.01)
Absolute change from Baseline to Day **176**	-1.1 (2.27)	-3.0 (2.49)
Day **183** NRS Score	4.7 (2.75)	3.1 (1.97)
Absolute change from Baseline to Day **183**	-1.1 (2.28)	-3.0 (2.41)
Day **190** NRS Score	4.7 (2.78)	3.1 (1.91)
Absolute change from Baseline to Day **190**	-1.1 (2.31)	-3.1 (2.25)
Day **197** NRS Score	4.7 (2.75)	3.1 (1.95)
Absolute change from Baseline to Day **197**	-1.1 (2.28)	-3.0 (2.28)

[0387]
[Table 46]

Table 34: Summary of Subjects achieving an IGA score of 0 or 1 to Week 12 and each visit during Follow-up period

Number and proportion of subjects achieving an IGA score of 0 or 1	Placebo (N=54)	300 mg mAb1 (N=55)
Week 12, Day 85	4 (7.4%)	22 (40.0%)
Week 14, Day 99	4 (7.4%)	22 (40.0%)
Week 16, Day 113	5 (9.3%)	18 (32.7%)
Week 18, Day 127	3 (5.6%)	20 (36.4%)
Week 20, Day 141	4 (7.4%)	17 (30.9%)
Week 22, Day 155	3 (5.6%)	17 (30.9%)
Week 24, Day 169	3 (5.6%)	13 (23.6%)
Week 26, Day 183	3 (5.6%)	15 (27.3%)
Week 28, Day 197	6 (11.1%)	16 (29.1%)

[0388]
[Table 47]

Table 35: Summary of Subjects achieving an EASI 50 Week 12 and each visit during Follow-up period

Number and proportion of subjects achieving an EASI score percent decrease of 50%	Placebo (N=54)	300 mg mAb1 (N=55)
Week 12, Day 85	19 (35.2%)	47 (85.5%)
Week 14, Day 99	19 (35.2%)	46 (83.6%)
Week 16, Day 113	18 (33.3%)	46 (83.6%)
Week 18, Day 127	18 (33.3%)	45 (81.8%)
Week 20, Day 141	18 (33.3%)	46 (83.6%)
Week 22, Day 155	16 (29.6%)	43 (78.2%)
Week 24, Day 169	18 (33.3%)	40 (72.7%)
Week 26, Day 183	19 (35.2%)	41 (74.5%)
Week 28, Day 197	23 (42.6%)	40 (72.7%)

[0389]
H. Conclusions

Subcutaneous administration of an anti-IL-4R antibody (mAb1) to adult patients with moderate-to-severe atopic dermatitis was generally safe and well tolerated after 12 weekly doses of 300 mg. Administration of mAb1 at 300 mg resulted in significant improvement in IGA, EASI, BSA, SCORAD and NRS pruritus through day 85 in both mean and absolute and percent change, as compared to baseline (see Tables 27 - 33). The proportion of patients achieving an IGA score of 0 or 1 at Day 85 for the 300 mg group was 40.0%, while the same number for placebo was 7.4% (Table 34). At Day 85, the proportion of patients who achieved an EASI score percent decrease of 50% ("EASI-50") was 85.5% for the 300 mg group, whereas the EASI-50 for placebo-treated patients at Day 85 was 35.2% (Table 35). The percent change in EASI score from baseline to week 12 of mAb1 was statistically significant from placebo group (-74.0% vs. -23.0%, p-value < 0.0001). The treatment group was statistically significantly different from

placebo group in all of the secondary efficacy endpoints. The following were the p-values for: IGA responder (0 or 1) (< 0.0001), EASI responder (< 0.0001), EASI absolute change from baseline (< 0.0001), absolute change of IGA from baseline (< 0.0001), percent change of IGA from baseline (< 0.0001), absolute change in BSA (< 0.0001), absolute change in SCORAD (< 0.0001), absolute change in Pruritus NRS (< 0.0001), and absolute change in 5-D pruritus scale from baseline to week 12 (< 0.0001) respectively.

[0414]

[Example 12]

Biomarker Analysis

Biomarker analysis was conducted on samples taken from subjects who participated in clinical trials of mAb1. In particular, IgE and thymus and activation chemokine (TARC) levels were measured in samples from patients at baseline and at different time points following initiation of study treatment(s). The Phadiatop™ test was performed to detect antigen-specific IgE. In addition, molecular profiling was carried out on skin lesions of patients who participated in clinical trials of mAb1.

[0420]

B. Administration of mAb1 to Subjects with Atopic Dermatitis

Biomarker levels were also measured in samples from two separate clinical trials involving subjects with atopic dermatitis (AD). In "Study A", AD subjects were administered either mAb1 (75, 150 or 300 mg) or placebo, on days 1, 8, 15 and 22 of the study (i.e., four weekly doses). In "Study B", AD subjects were administered 150 mg or 300 mg of mAb1, or placebo, on days 1, 8, 15 and 22 of the study (i.e., four weekly doses) (see Example 7 herein). All administrations for both studies were subcutaneous (SC). Samples for biomarker analysis were collected from the antibody- and placebo-treated subjects from both studies at days 1 (baseline), 4, 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71 and 85 (or early termination). Levels of IgE, TARC, lactate dehydrogenase (LDH), and antigen-specific IgE (Phadiatop) were measured in each sample.

[0421]

Serum TARC was measured using a validated assay (Human CCL17/TARC Quantikine ELISA kit, R&D Systems; validation and assays performed by Quest Diagnostics). Total serum IgE levels were determined using the ImmunoCAP® Total IgE test (Thermo Scientific FDA cleared test; performed by Quest Diagnostics). Lactate dehydrogenase (LDH) was measured using the Roche Modular test (FDA cleared; performed by Covance Central Laboratories). Phadiatop® (Thermo Scientific FDA

cleared test) assays were performed by Viracor-IBT. Two-sample median test was used to compare the biomarker changes from baseline with mAb1 to placebo.

[0422]

Mean baseline levels of serum TARC, total IgE and LDH for all AD patients enrolled in study 'B' were higher than the reported upper limit of normal (ULN) (Table 47 and Figure 51).

[0423]

[Table 59]

Table 47: Summary of Baseline Biomarker Characteristics

Biomarker	Mean Baseline (SEM) All patients (n=37)	Mean Baseline (SEM) Placebo (n=10)	Mean Baseline (SEM) 150 mg DPL (n=14)	Mean Baseline (SEM) 300 mg DPL (n=14)
EASI	28.4 (2.56)	25.64 (4.34)	32.55 (4.96)	25.91 (3.71)
TARC (pg/mL)	6914.9 (2001.3)	7001 (2669.8)	9162.2 (4851.7)	4601.4 (1957.3)
IgE (kU/L)	8038.3 (2052.2)	15026.5 (4748.6)	7231.9 (2634.1)	2931.7 (1383.4)
Phadiatop®	34/36 patients were +	All +	All +	2 patients were -
LDH (U/L)	240.4 (13.4)	296.7 (28.8)	226.1 (21)	212.5 (16.1)
Eos (10^9 cells/L)	0.50 (0.06)	0.65 (0.13)	0.49 (0.09)	0.41 (0.11)
Eos (%)	6.37 (0.71)	8.03 (1.06)	6.17 (1.18)	5.29 (1.32)

[0424]

Mean baseline eosinophil levels were at the high end of the reference range (Table 47). All but 2 patients with available data tested positive for the Phadiatop test. Both of these patients also had normal total serum IgE levels. Phadiatop results were unavailable for one patient.

[0425]

A broad spectrum of baseline TARC and IgE was observed in the enrolled moderate-to-severe AD population. 27/36 of patients had serum TARC levels >1000 pg/mL (-twice the mean levels reported for healthy volunteers (Figure 51A). 32/36 of patients had IgE levels ≥ 150 kU/L (a cutoff often cited to distinguish extrinsic and intrinsic AD) (Figure 51B). 17/37 had LDH levels above 234 U/L (Figure 51C). No patients had LDH levels below 100 U/L.

[0426]

Using local linear regression, an overall mAb1 treatment effect (percent change from baseline) on total serum IgE was observed compared to placebo in both dose groups ($p < 0.0001$) (Figure 52). Total serum IgE levels decreased with mAb1 treatment, while an overall increase was observed at the end of the study in the placebo treated

group.

[0427]

The median percent change in IgE levels from baseline for each group from both studies A and B (combined data) is summarized in Table 48.

[0428]

[Table 60]

Table 48: Median Percent Change in IgE Level from Baseline (Study A and B Combined)

	subcutaneous (SC)			
		mAb1		
	Placebo	75 mg	150 mg	300 mg
*Baseline	-	-	-	-
Day 4	2.7	TBD	4.3	0.0
*Day 8	0.2	TBD	17.6	-2.2
*Day 15	25.7	TBD	13.2	0.0
*Day 22	19.0	TBD	-4.4	-2.1
Day 25	28.4	TBD	-7.4	-9.5
Day 29	32.0	TBD	0.2	-1.6
Day 36	43.0	TBD	-5.5	-12.1
Day 43	43.0	TBD	-11.2	-4.8
Day 50	28.9	TBD	-13.7	-17.3
Day 57	54.2	TBD	-11.7	-18.3
Day 64	51.2	TBD	-21.6	-14.3
Day 71	37.5	TBD	-15.4	-22.3
Day 85	41.7	TBD	-16.8	-23.9

* Denotes days when drug or placebo was administered

[0429]

As shown in Table 48 and Figure 52, a statistically significant decrease in IgE was observed in samples from mAb1 -treated subjects compared to placebo. The median percent change IgE at day 85 was -23.9% in patients treated with 300 mg mAb1, compared to a 41.7% increase in the placebo group ($p < 0.0001$). The median percent change from baseline in the 150 mg group compared to placebo was significant at all

time-points from days 29-85 ($p < 0.03$). The median percent change from baseline in the 300 mg group compared to placebo was significant at all time-points from days 15-85 ($p < 0.04$).

[0430]

Using local linear regression, an overall treatment effect was observed for LDH. There was a statistically significant decrease in LDH in the 300 mg treatment group ($p = 0.0051$) (Figure 53). Median percent change was not statistically significant at any single time point, however, a temporal trend was observed ($p = 0.008$).

[0431]

mAb1 treatment rapidly suppressed serum TARC levels in AD patients (Figure 54). The median percent change in TARC levels from baseline for each group from both studies (combined data) is summarized in Table 49.

[0432]
[Table 61]

Table 49: Median Percent Change in TARC Level from Baseline (Study A and B Combined)

	subcutaneous (SC)			
		mAb1		
	Placebo	75 mg	150 mg	300 mg
*Baseline	-	--	-	-
Day 4	-7.9	TBD	-37.0	-20.8
*Day 8	-1.1	TBD	-24.8	-37.5
*Day 15	-19.3	TBD	-61.0	-56.6
*Day 22	-5.0	TBD	-64.4	-73.1
Day 25	-25.5	TBD	-69.5	-78.5
Day 29	-22.7	TBD	-79.9	-70.9
Day 36	-18.3	TBD	-78.1	-77.9
Day 43	-35.3	TBD	-86.3	-72.3
Day 50	-28.9	TBD	-82.2	-67.4
Day 57	-37.4	TBD	-55.2	-71.4
Day 64	-33.2	TBD	-45.5	-78.1
Day 71	-43.0	TBD	-28.6	-60.3
Day 85	-45.2	TBD	-28.3	-37.3

* Denotes days when drug or placebo was administered

[0433]

A statistically significant reduction in serum TARC was observed in patients treated with 300 mg mAb1 compared to placebo ($p < 0.0001$; local linear regression analysis). Statistically significant suppression was maintained through day 50 in patients treated with 300 mg mAb1, approximately one month after the last dose (administered on study day 21). The 150 mg group achieved comparable magnitude of suppression, but levels were observed to increase sooner than in the 300 mg group. Statistically significant suppression (median percent change TARC from baseline compared to placebo) was observed at days 36 and 43 in the 150 mg group ($p < 0.03$), as well as days 22, 25, 29, 36, and 50 with the 300 mg group ($p < 0.04$).

[0434]

Intra-patient variability of TARC levels was observed over the course of the study in placebo-treated patients. Data from only 4 placebo-treated patients was available at the end of the study, due to a high dropout rate in that group.

[0435]

In conclusion, TARC, IgE and LDH, biomarkers associated with Th2 inflammation and/or AD disease activity, were all suppressed by mAb1 treatment in AD patients. mAb1 rapidly decreased serum TARC levels in AD patients, compared to placebo. Duration of suppression appeared to be dose-related and data suggested that the effect might be sustained even after drug discontinuation. Total serum IgE levels significantly declined in mAb1 treated patients. IgE continued to decline (median percent change) in the 300 mg group after the treatment phase, suggesting that maximal IgE suppression had not yet been achieved. A consistent reduction in LDH levels from baseline was observed in patients treated with mAb1. A direct link between LDH and IL-4 and IL-13 is unknown, but its association with disease severity suggested LDH might be a measure of the extent of skin damage in AD patients. The suppression of TARC and IgE demonstrated that mAb1 is a potent inhibitor of Th2 inflammation.

[0436]

Correlations among biomarkers and AD-associated parameters

In Study "B" (see Example 7), patients with severe AD were given 150 or 300 mg mAb1 or placebo (PBO) weekly for four weeks. Pruritus was measured using twice-daily pruritus Numeric Rating Scale (NRS; ranging from 0-10) to generate an average weekly NRS score & a bi-weekly 5-D Pruritus Scale assessments. The 5-D scale is a 5 question tool used to assess multiple dimensions of itch: degree, duration, direction, disability, and distribution. Mean baseline NRS & 5-D scores were 5.5 & 19, respectively. The average weekly NRS scores rapidly decreased (mean % change from baseline) by 31.9% at week 2 ($p < 0.02$), & 55.2% at week 7 ($p = 0.01$) in the 300 mg group vs +1.3% and -17.3% respectively in the PBO group. Rapid reduction in 5-D scores was also observed in patients treated with 300 mg mAb1 (mean % change -28.2% at day 15, $p = 0.0009$; -37.1% at day 29, $p = 0.0007$; -42.5% at day 43, $p = 0.012$; +3.6%, +8.1% & -9.4% respectively in the PBO group). Serum levels of CCL17, a marker of IL4/IL13 activity, also rapidly declined on treatment. Both CCL17 and pruritus were suppressed for several weeks following the end of treatment. Table 50 shows the correlation of pruritus (5D and NRS) with outcomes of dermatitis (EASI) and CCL17.

[0437]
[Table 62]

Table 50

Time point	5D correlations				NRS correlations			
	EASI		CCL17		EASI		CCL17	
	Spearman *r*	*P*	Spearman *r*	*P*	Spearman *r*	*P*	Spearman *r*	*P*
Actual Values								
Baseline	0.41	0.0111	0.46	0.0044	0.35	0.0321	0.42	0.0117
Day 29	0.62	0.0001	0.55	0.0024	0.64	<0.0001	0.12	0.5413
Percent change from baseline								
Day15	0.65	<0.0001	0.46	0.0089	0.51	0.0012	0.32	0.0795
Day29	0.61	<0.0001	0.48	0.0105	0.61	<0.0001	0.11	0.5640

[0438]

Overall, for all treatment groups, the 5D score significantly correlated with CCL17 ($r = 0.46$, $p = 0.004$ at baseline; $r = 0.55$, $p = 0.002$ at day 29) & EASI scores in this study ($r = 0.41$, $p = 0.011$ at baseline; 0.62, $p < 0.0001$ at day 29). The percent change in 5D significantly correlated with the percent change from baseline in EASI ($r = 0.65$, $p < 0.0001$ for day 15; and $r = 0.61$, $p < 0.0001$ for day 29) and CCL17 ($r = 0.46$, $p = 0.0089$ for day 15; and $r = 0.48$, $p = 0.0105$ for day 29) for the overall treatment groups at Days 15 and 29. Treatment groups were also individually assessed for correlation of Pruritus 5D with EASI and CCL17. At day 15, only the 150 mg group demonstrated strong and significant correlation between the percent change in EASI and percent change in 5D ($r = 0.81$, $p = 0.0005$). Similarly at day 29, the only significant correlation was for the 150 mg group ($r = 0.57$, $p = 0.0036$). Although there was a significant overall correlation between percent change in CCL17 and percent change in 5D score at both day 15 and day 29, none of the individual treatment groups showed such a correlation at either day.

[0439]

Pruritus severity, assessed using the NRS, showed moderate to strong correlations with EASI that were significant. However, NRS values correlated with CCL17 values only at baseline, with no significant correlation for percent change from baseline. The rapid & sustained improvement in pruritus observed in adult AD patients treated with mAb1 suggests IL-4/IL-13 signaling is a key mechanism for AD pruritus. The correlation between pruritus and CCL17 levels highlights the relationship between IL-4/IL-13 mediated inflammation, AD disease activity & pruritus in severe AD.

[0440]

C. Repeated Administration of mAb1 to Subjects with moderate-to-severe Atopic Dermatitis

IgE and TARC levels were measured in samples from a clinical trial involving subjects with moderate-to-severe atopic dermatitis (AD). AD subjects were administered 300 mg of mAb1, or placebo, on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78 of the study (i.e., 12 weekly doses) (see Example 10 herein). All administrations for both studies were subcutaneous (SC). Serum samples for biomarker analysis were collected from the antibody- and placebo-treated subjects from both studies at days 1 (baseline), 8, 15, 22, 25, 29, 36, 43, 50, 57, 64, 71, 85, 99, 113, 127, 141, 155, 169, 183 and 197 (end of study) or early termination. Levels of IgE, TARC and antigen-specific IgE (Phadiatop™ test) were measured in each sample.

[0441]

TARC is a chemokine induced by IL-4/IL-13, shown to be strongly associated with disease severity of AD, and may be involved in pathogenesis of the disease. Baseline TARC levels were assessed for potential predictive value for treatment response. Post-treatment samples were evaluated for pharmacodynamics effect of mAb1 on TARC.

[0442]

Patients with AD often have elevated IgE. Total IgE levels have been found to correlate with AD severity and may be involved in the pathogenesis of the disease. Baseline IgE levels were assessed for potential predictive value for treatment response. Post-treatment samples were evaluated for pharmacodynamics effects of mAb1 on total IgE.

[0443]

The Phadiatop™ test is an invitro diagnostic screening tool used to detect antigen-specific IgE for common inhalants. Baseline results of the Phadiatop™ test were assessed for potential predictive value for treatment response. Post-treatment samples were evaluated for pharmacodynamics effects of mAb1 on the Phadiatop™ antigen panel.

[0444]

In line with the results obtained from earlier clinical trials (see sections A and B above), the TARC and IgE levels decreased and remained suppressed below baseline through the 16-week post-treatment follow-up period (Figures 55 - 56).

[0445]

Greater magnitude of IgE suppression was observed with 12 weeks of 300 mg mAb1 treatment during a 16-week followup (median -57%) as compared 4 weeks of mAb1. Magnitude of TARC suppression was comparable at the end-of-treatment after 12 weeks

(median -83%) and weeks (median -76%) of mAb1 treatment.