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(54) **Title**: METHODS FOR TREATING PSORIASIS USING AN ANTI-IL-23 ANTIBODY

V_H1 (SEQ ID NO: 1)

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNEYYADSVKGR
CDR 1 CDR 2

FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGYTSSWYPDAFDIWGQGTMVTVSS
CDR 3

V_L1 (SEQ ID NO: 2)

QSVLTQPPSVSGAPGQRVTISCTGSSSNTGAGYDVHWYQQVPGTAPKLLIYGSGNRPS
CDR 1 CDR 2

GVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSGWVFGGGTRLTVL
CDR 3

Figure 11

(57) **Abstract**: The invention relates to products and methods for treating psoriasis. The products relate to antibodies that inhibit native human IL-23 while sparing IL-12. One example describes a Phase 1, randomized, double- blind, placebo-controlled, ascending single dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of an anti-IL-23 antibody (AMG 139) in healthy subjects and subjects with moderate to severe psoriasis.

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METHODS FOR TREATING PSORIASIS USING AN ANTI-IL-23 ANTIBODY

Field of the Invention

[0001] The invention relates to products and methods for treating psoriasis. The products relate to antibodies that inhibit native human IL-23 while sparing IL-12.

Background

[0002] Psoriasis is a common chronic idiopathic inflammatory disease of skin. It affects 1% to 2% of Caucasians including ~25 million people in North America and Europe. Both genetic and environmental factors play key roles in the pathogenesis of psoriasis, which is noted histopathologically by marked thickening of the epidermis, alterations in keratinocyte proliferation and differentiation, and a genetic program similar to that observed in wound repair. The trigger for this altered keratinocyte response is thought to be activation of the cellular immune system, and numerous studies have implicated T-cells, dendritic cells and various inflammatory cytokines and chemokines in disease pathogenesis (Nestle FO, Kaplan DH, et al. Psoriasis. *N Engl J Med.* 2009;361(5):496-509; Griffiths CE and Barker JN. *Lancet.* 2007;370(9583):263-271; Lowes MA, Bowcock AM, et al. *Nature.* 2007;445(7130):866-873; Nickoloff BJ and Nestle FO. *J Clin Invest.* 2004;113(12):1664-1675.

[0003] Interleukin 23 (IL-23), expression is increased in psoriatic lesional tissue. IL-23 is a heterodimeric cytokine and a potent inducer of pro-inflammatory cytokines. IL-23 is related to the heterodimeric cytokine Interleukin 12 (IL-12) both sharing a common p40 subunit. In IL-23, a unique p19 subunit is covalently bound to the p40 subunit. In IL-12, the unique subunit is p35 (Oppmann et al., Immunity, 2000, 13: 713-715). Like IL-23 is expressed by antigen presenting cells (such as dendritic cells and macrophages) in response to activation stimuli such as CD40 ligation, Toll-like receptor agonists and pathogens. IL-23 binds a heterodimeric receptor comprising an IL-12Rβ1 subunit (which is shared with the IL-12 receptor) and a unique receptor subunit, IL-23R.

[0004] IL-23 acts on activated and memory T cells and promotes survival and expansion of the T cell subset, Th17. Th17 cells produce proinflammatory cytokines including IL-6, IL-17, TNFα, IL-22 and GM-CSF. IL-23 also acts on natural killer cells, dendritic cells and macrophages to induce pro-inflammatory cytokine expression. Unlike IL-23, IL-12 induces the differentiation of naïve CD4+ T

cells into mature Th1 IFNγ-producing effector cells, and induces NK and cytotoxic T cell function by stimulating IFNγ production. Th1 cells driven by IL-12 were previously thought to be the pathogenic T cell subset in many autoimmune diseases, however, more recent animal studies in models of inflammatory bowel disease, psoriasis, inflammatory arthritis and multiple sclerosis, in which the individual contributions of IL-12 versus IL-23 were evaluated have firmly established that IL-23, not IL-12, is the key driver in autoimmune/inflammatory disease (Ahern et al., Immun. Rev. 2008 226:147-159; Cua et al., Nature 2003 421:744-748; Yago et al., Arthritis Res and Ther. 2007 9(5): R96). It is believed that IL-12 plays a critical role in the development of protective innate and adaptive immune responses to many intracellular pathogens and viruses and in tumor immune surveillance. See Kastelein, et al., Annual Review of Immunology, 2007, 25: 221-42; Liu, et al., Rheumatology, 2007, 46(8): 1266-73; Bowman et al., Current Opinion in Infectious Diseases, 2006 19:245-52; Fieschi and Casanova, Eur. J. Immunol. 2003 33:1461-4; Meeran et al., Mol. Cancer Ther. 2006 5: 825-32; Langowski et al., Nature 2006 442: 461-5. As such, IL-23 specific inhibition (sparing IL-12 or the shared p40 subunit) should have a potentially superior safety profile compared to dual inhibition of IL-12 and IL-23.

[0005] IL-23p19 and IL-12/23p40 mRNA are increased in psoriatic lesional skin as compared to non-lesional skin; 22- and 12-fold mean increase, respectively. The expression of IL-12p35 mRNA did not differ significantly between paired lesional and nonlesional skin (Lee E, Trepicchio WL, et al. *J Exp Med.* 2004;199(1):125-130.). These data suggest IL-23 is upregulated in psoriatic lesional tissue while IL-12 is not. IL-23 protein has been demonstrated to be upregulated in psoriatic lesional skin as well through immunohistochemical analysis. Anti-IL-23p19 antibody staining showed increased expression in both the epidermis and the dermis in lesional psoriatic skin as compared to normal (and nonlesional) skin (Piskin G, Sylva-Steenland RM, et al. In vitro and in situ expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions: enhanced expression in psoriatic skin. *J Immunol.* 2006;176(3):1908-1915). IL-23 levels decrease with clinical improvement of PsO following effective treatment of disease (either UV or anti-TNF treatment) providing a direct correlation between overproduction of IL-23 and active psoriasis (Fitch E, Harper E, et al. Pathophysiology of psoriasis: recent advances on IL-23 and Th17 cytokines. *Curr Rheumatol Rep.* 2007;9(6):461-4).

[0006] A genome-wide association study was conducted in psoriasis patients using a collection of > 25,000 primarily functional SNPs in 3 independent case-control sample sets. In this study they found a highly significant association with a SNP in the 3'UTR of IL-12/23p40. Multiple SNPs in the IL-12

(p35) and IL-23 (p19) ligand and receptor chains (IL-12Rβ1, IL-12Rβ2, and IL-23R) were individually genotyped. Two SNPs in the IL-23R were highly associated with psoriasis while there was no association with the other ligand and receptor chains (Cargill M, Schrodi SJ, et al. *Am J Hum Genet.* 2007;80(2):273-290). The finding that common variants in both IL-12/23p40 and IL-23R are associated with psoriasis risk provides genetic evidence that the IL-23 pathway plays an important role in psoriasis pathogenesis.

[0007] Current approved therapies for psoriasis include topical agents (eg, corticosteroids, coal tar preparations, retinoids, phototherapy); systemic therapies (eg, methotrexate, retinoids, cyclosporin); and biologics (eg, etanercept, adalimumab, alefacept, ustekinumab). Despite these available therapies many patients remain untreated, do not respond to therapy, or suffer from toxicities associated with systemic or phototherapy, with significant skin involvement and disability.

[0008] It is contemplated herein that there is a need for new modalities for the treatment of psoriasis that specifically target IL-23 without the potential risks associated with inhibition of IL-12. Provided herein are methods for the treatment of psoriasis using fully human therapeutic agents that are able to inhibit native human IL-23 while sparing IL-12.

Summary

[0009] Provided herein are methods of treating psoriasis in a subject in need thereof comprising administering to the subject an anti-IL-23 antibody in an amount and at an interval of: 15 – 54 mg every 0.5 – 1.5 months; 55 – 149 mg every 1.5 – 4.5 months; 150 – 299 mg every 4 – 8 months; or 300 – 1100 mg every 4 – 12 months. In some embodiments, the amount and interval are: 15 – 21 mg every 0.5 – 1.0 month; 55 – 70 mg every 1.5 – 3.0months; 150 – 260 mg every 4 – 6 months; or 300 – 700 mg every 4 – 8 months. In some embodiments, the amount and interval are: 21 mg every month; 70 mg every 3 months; 210mg every 6 months; or 700 mg every 6 months. In some embodiments, the amount and interval are: 210 mg every 3 months or 700 mg every 3 months. In some embodiments, the amount and interval are: 210 mg every 1 month or 700 mg every 1 month. In some embodiments of the methods, the anti-IL23 antibody is administered IV. In some embodiments of the methods, the anti-IL23 antibody is administered SC. In some embodiments of the methods, the anti-IL-23 antibody is AMG 139.

[0010] Also provided herein are methods of treating psoriasis in a subject in need thereof comprising administering to the subject an amount of an anti-IL-23 antibody in an amount and at an

interval sufficient to achieve and/or maintain a quantity of anti-IL-23 antibody per volume of serum of between 12.5 ng /ml and 1000 ng/ml. In some embodiments, the quantity of an anti-IL-23 antibody per volume of serum is at least 10 ng/ml. In some embodiments, the quantity of an anti-IL-23 antibody per volume of serum is selected from the group consisting of: at least 25 ng/ml; at least 50 ng/ml; at least 60 ng/ml; at least 70 ng/ml; at least 75 ng/ml; and at least 80 ng/ml. In some embodiments, the quantity of an anti-IL-23 antibody per volume of serum is between 85 ng/ml and 100 ng/ml. In some embodiments, the quantity of an anti-IL-23 antibody per volume of serum is between 70 ng/ml and 150 ng/ml. In some embodiments the quantity of an anti-IL-23 antibody per volume of serum is is between 50 ng/ml and 250 ng/ml. In some embodiments, the quantity of an anti-IL-23 antibody per volume of serum is is between 40 ng/ml and 500 ng/ml. In some embodiments, the quantity of an anti-IL-23 antibody per volume of serum is between 25 ng/ml and 750 ng/ml. In some embodiments, the quantity of an anti-IL-23 antibody per volume of serum is between 10 ng/ml and 1,000 ng/ml. In some embodiments of the methods, the anti-IL23 antibody is administered IV. In some embodiments of the methods, the anti-IL23 antibody is administered SC. In some embodiments of the methods, the anti-IL-23 antibody is AMG 139.

Brief Description of the Drawings

[0011] Figure 1 presents the results of the pharmacokinetic analysis of an ascending single dose study of subcutaneous administration of AMG 139 in healthy subjects (HS). The results shown illustrate the mean (± SD) serum AMG 139 concentration-time profiles.

[0012] Figure 2 presents the results of the pharmacokinetic analysis of an ascending single dose study of intravenous administration of AMG 139 in healthy subjects (HS). The results shown illustrate the mean (± SD) serum AMG 139 concentration-time profiles.

[0013] Figure 3 presents the results of the pharmacokinetic analysis of an ascending single dose study of subcutaneous AMG 139 administration in psoriasis subjects (PsO). The results shown illustrate the mean (± SD) serum AMG 139 concentration-time profiles.

[0014] Figure 4 presents the results of the pharmacokinetic analysis of an ascending single dose study of intravenous AMG 139 administration in psoriasis subjects (PsO). The results shown illustrate the mean (± SD) serum AMG 139 concentration-time profiles.

[0015] Figure 5 presents the results of Psoriasis Area and Severity Index (PASI) score assessment in PsO subjects from the single ascending dose study. The results shown illustrate the mean PASI score (± SD) at time points throughout the study.

[0016] Figure 6 presents the results of Psoriasis Area and Severity Index (PASI) score assessment (normalized to baseline) in PsO subjects from the single ascending dose study. The results shown illustrate the mean improvement of PASI score from baseline (± SD) at time points throughout the study.

[0017] Figure 7 presents the pharmacokinetic structural model used in developing the AMG 139 quantitative population PK model based on data from Example 1.

[0018] Figure 8 presents the results of a diagnostic visual predictive check of the AMG 139 population PK model. The results shown illustrate the mean (solid line) and 90% confidence interval (dashed line) AMG 139 concentration-time profile after simulating 1000 clinical trials. Each point represents actual, observed concentrations from subjects.

[0019] Figure 9 presents the results of multiple diagnostic visual predictive checks of the AMG 139 population PK model. The results illustrate correlations between observed AMG 139 concentrations and that of population and individual predicted concentrations, as well as the weighted residuals of model fitting between population predicted concentrations and time.

[0020] Figure 10 presents the results of a correlation analysis between body weight and PK parameters. The results illustrate a positive correlation in individual CL and V with body weight for the combined population of healthy and PsO subjects.

[0021] Figure 11 presents the amino acid sequences of AMG 139 heavy and light chain variable regions.

Detailed Description

[0022] Provided herein are methods for treating psoriasis in a subject in need thereof comprising administering to the subject an amount of a human monoclonal antibody that specifically binds IL-23. In some embodiments, the anti-IL-23 antibody specifically binds IL-23 but spares IL-12.

[0023] The terms "treating", and "treatment" and the like are used herein to generally mean obtaining a desired pharmacological, physiological or therapeutic effect. The effect may be prophylactic in terms of preventing or partially preventing a disease, symptom or condition thereof

and/or may be therapeutic in terms of a partial or complete cure of a disease, condition, symptom or adverse effect attributed to the disease. The term "treatment" as used herein covers any treatment of a disease in a mammal, particularly a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; or (c) relieving the disease, i.e., causing regression of the disease and/or its symptoms or conditions. The invention is directed towards treating a patient's suffering from disease related to pathological inflammation. The present invention is involved in preventing, inhibiting, or relieving adverse effects attributed to pathological inflammation over long periods of time and/or are such caused by the physiological responses to inappropriate inflammation present in a biological system over long periods of time.

[0024] In one aspect, the present invention provides methods of treating a subject. The method can, for example, have a generally salubrious effect on the subject, *e.g.*, it can increase the subject's expected longevity. Alternatively, the method can, for example, treat, prevent, cure, relieve, or ameliorate ("treat") a disease, disorder, condition, or illness ("a condition"). In one embodiment, the present invention provides a method of treating a condition in a subject comprising administering the pharmaceutical composition comprising an specific antibody to the subject, wherein the condition is treatable by reducing the activity (partially or fully) of IL-23 in the subject. Treating encompasses both therapeutic administration (i.e., administration when signs and symptoms of the disease or condition are apparent) as well prophylactic or maintenance therapy (i.e., administration when the disease or condition is quiescent), as well as treating to induce remission and/or maintain remission. Accordingly, the severity of the disease or condition can be reduced (partially, significantly or completely), or the signs and symptoms can be prevented or delayed (delayed onset, prolonged remission, or quiescence).

[0025] Among the conditions to be treated in accordance with the present invention are conditions in which IL-23 is associated with or plays a role in contributing to the underlying disease or disorder or otherwise contributes to a negative symptom. Such conditions include skin disorders such as psoriasis, plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis, dermatitis and atopic dermatitis.

[0026] The term "efficacy" as used herein in the context of a dosage regimen refers to the effectiveness of a particular treatment regimen. Efficacy can be measured based on change the course of the disease in response to an agent of the present invention. In one embodiment, an antigen binding protein (for example, an anti-IL-23 antibody) is administered to the subject in an amount and for a time

sufficient to induce an improvement, preferably a sustained improvement, in at least one indicator that reflects the severity of the disorder that is being treated. Various indicators that reflect the extent of the subject's illness, disease or condition may be assessed for determining whether the amount and time of the treatment is sufficient. Such indicators include, for example, clinically recognized indicators of disease severity, symptoms, or manifestations of the disorder in question.

[0027] In one embodiment, an improvement is considered to be sustained if the subject exhibits the improvement on at least two occasions separated by two to four weeks. In another embodiment, an improvement is considered to be sustained if the subject exhibits the improvement on at least two occasions separated by two to four months; in a further embodiment, an improvement is considered to be sustained if the subject exhibits the improvement on at least two occasions separated by six to twelve months. The degree of improvement generally is determined by a physician, who may make this determination based on signs, symptoms, biopsies, or other test results, and who may also employ questionnaires that are administered to the subject, such as quality-of-life questionnaires developed for a given disease.

[0028] The IL-23 specific antibody may be administered to achieve an improvement in a subject's condition. Improvement may be indicated by a decrease in an index of disease activity, by amelioration of clinical symptoms or by any other measure of disease activity. On such index of disease is the psoriasis area and severity index (PASI). PASI is a measurement of of the average redness, thickness, and scaliness of the lesions, each graded on a scale of 0-4, weighed by the area of involvement. Psoriasis Target Lesion Assessment Score, is an index for assessing the severity of individual skin lesions. The score is based on the sum of the evaluation of plaque elevation, amount and degree of scaling or degree of erythema, and target lesion response to treatment. Another disease index is the National Psoriasis Foundation Psoriasis Score (NSF-PS). The degree of improvement generally is determined by a physician, who may make this determination based on signs, symptoms, (such as a phychian global assessment (PGA)), an overall lision assessment (OLA), biopsies, whole body photographs, or other test results, and who may also employ questionnaires that are administered to the subject, such as quality-of-life questionnaires developed for a given disease.

[0029] In one embodiment, an improvement is considered to be sustained if the subject exhibits the improvement on at least two occasions separated by two to four weeks. In another embodiment, an improvement is considered to be sustained if the subject exhibits the improvement on at least two occasions separated by two to four months; in a further embodiment, an improvement is considered to

be sustained if the subject exhibits the improvement on at least two occasions separated by six to twelve months. In another embodiment, improvement is considered to be achieved when the subject exhibits at least 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100% improvement in PASI score.

[0030] Treatment of a subject with an IL-23 specific antibody may be given in an amount and/or at sufficient interval to achieve and/or maintain a certain quantity of IL-23-specific antibody per volume of serum, using, for example, an assay as described herein. For example, the heterodimer specific antibody is given to achieve from 12.5 ng/ml to 1000ng/ml. In one embodiment, the heterodimer specific antibody is given to achieve at least 12.5 ng/ml, 25 ng/ml, 50 ng/ml, 60 ng/ml, 70 ng/ml, 75 ng/ml, 80 ng/ml, 85 ng/ml, 90 ng/ml, 95 ng/ml, 100 ng/ml, 150 ng/ml, 200 ng/ml, 500 ng/ml, or 990 ng/ml. Those of skill in the art will understand that the amounts given here apply to a full-length antibody or immunoglobulin molecule; if an antigen binding fragment thereof is used, the absolute quantity will differ from that given in a manner that can be calculated based on the molecular weight of the fragment.

[0031] Treatment of a subject with an IL-23 specific antibody may be given in an amount and at an interval of 15 – 54 mg every 0.5 – 1.5 months; 55 – 149 mg every 1.5 – 4.5 months; 150 – 299 mg every 4 – 8 months; or 300 – 1100 mg every 14 – 8 months. In one embodiment the amount and interval are selected from the group consisting of: 21 mg every month; 70 mg every 3 months; 210 mg every 6 months; or 700 mg every 6 months.

[0032] Both ubcutaneous and intravenous administration of AMG139 significantly reduced the symptoms of psoriasis as measured by the PASI scoring system. In some embodiments, administration of AMG139 at the dosages and administration schedules described above may be used to reduce the PASI score in a patient having psoriasis by at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100%.

[0033] It is understood that the methods of treating the diseases described herein would administer an effective amount of an anti-IL-23 antibody. Depending on the indication to be treated, a therapeutically effective amount is sufficient to cause a reduction in at least one symptom of the targeted pathological condition by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, relative to untreated subjects.

[0034] Administration and dosage regimens of an anti-IL-23 antibody can be adjusted to provide an effective amount for an optimum therapeutic response. For example, a single bolus can be administered, several divided doses can be administered over time or the dose can be proportionally

reduced or increased as indicated by the exigencies of the therapeutic situation. The anti-IL-23 antibody may be administered by any suitable technique, including but not limited to, parenterally, topically, or by inhalation. If injected, the pharmaceutical composition can be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal or cutaneous routes (including intra-, trans- or sub- dermal, and subcutaneous), by bolus injection, or continuous infusion. In some embodiments, the pharmaceutical composition is administered by an intravenous route. In some embodiments the pharmaceutical composition is administered by a subcutaneous route. In further embodiments, the compositions are administered by oral, buccal, rectal, intratracheal, gastric, or intracranial routes. Localized administration, *e.g.* at a site of disease or injury is contemplated, for example, by enema or suppository for conditions involving the gastrointestinal tract. Also contemplated are transdermal delivery and sustained release from implants. Delivery by inhalation includes, for example, nasal or oral inhalation, use of a nebulizer, inhalation of the antagonist in aerosol form, and the like. Other alternatives include eyedrops; oral preparations including pills, syrups, lozenges or chewing gum; and topical preparations such as lotions, gels, sprays, and ointments.

[0035] Advantageously, IL-23 antibodies are administered in the form of a composition comprising one or more additional components such as a physiologically acceptable carrier, excipient or diluent. Optionally, the composition additionally comprises one or more physiologically active agents for combination therapy. A pharmaceutical composition may comprise an anti-IL-23 antibody together with one or more substances selected from the group consisting of a buffer, an antioxidant such as ascorbic acid, a low molecular weight polypeptide (such as those having fewer than 10 amino acids), a protein, an amino acid, a carbohydrate such as glucose, sucrose or dextrins, a chelating agent such as EDTA, glutathione, a stabilizer, and an excipient. Neutral buffered saline or saline mixed with conspecific serum albumin are examples of appropriate diluents. In accordance with appropriate industry standards, preservatives such as benzyl alcohol may also be added. The composition may be formulated as a lyophilizate using appropriate excipient solutions (*e.g.*, sucrose) as diluents. The anti-IL-23 antibody can be provided at a concentration of 50 to 200 mg/ml. Exemplary formulations useful for the present invention are those that include a glutamic acid, citric acid or acetic acid buffer as an appropriate pH, from 4.5 to 5.2, an excipient such as sucrose, glycine, proline, glycerol, and/or sorbitol at an appropriate concentration such as 1 to 20% (w/v), and a surfactant such as a non-ionic surfactant like polysorbate (polysorbate 20 or 80) or poloxamers (poloxamer 1888) at an appropriate concentration of 0.001% - 0.1% (w/v). Such formulations are disclosed in US Patent No. 6171586 and

WIPO Published Applications Nos: WO20100027766 and WO2011088120. In some embodiments, the formulations comprise sodium acetate, sucrose and polysorbate 20. In some embodiments, the formulations comprise 70 mg/mL AMG 139, 10 mM sodium acetate, 9% (w/v) sucrose and 0.004% (w/v) polysorbate 20, at pH 5.2. Suitable components are nontoxic to recipients at the dosages and concentrations employed. Further examples of components that may be employed in pharmaceutical formulations are presented in any Remington's Pharmaceutical Sciences including the 21st Ed. (2005), Mack Publishing Company, Easton, PA.

[0036] Kits for use by medical practitioners include an anti-IL-23 antibody and a label or other instructions for use in treating any of the conditions discussed herein. In one embodiment, the kit includes a sterile preparation of one or more IL-23 binding antigen binding proteins, which may be in the form of a composition as disclosed above, and may be in one or more vials.

[0037] Particular embodiments of methods of the invention involve the use of an anti-IL-23 antibody and one or more additional IL-23 antagonists, as described in US Patents US 7,491,391; US 7,807,414; US7,872,102; US7,807,160; US8362212; US7,935,344; US 7,790,862; US2012282269; US Published Patent Applications US 2009-0123479; US 20120128689; and US2012264917 and WIPO Publications WO1999/05280, WO2007/0244846, WO2007/027714, WO 2007/076524, WO2007/147019, WO2008/103473, WO 2008/103432, WO2009/043933, WO2009/082624 WO 12/009760.

[0038] Also provided are IL-23 antibodies administered alone or in combination with other agents useful for treating the condition with which the patient is afflicted. Topical medications (e.g., steroids, coal tar, anthralin, Dead Sea salts, various natural oils, vitamin D3 and its analogs, sunshine, topical retinoids), phototherapy (e.g., ultraviolet light, photochemotherapy (PUVA)), and internal medications (e.g., methotrexate, systemic steroids, oral retinoids, cyclosporine,). When multiple therapeutics are co-administered, dosages may be adjusted accordingly, as is recognized or known in the pertinent art.

[0039] In every case where a combination of molecules and/or other treatments is used, the individual molecule(s) and/or treatment(s) can be administered in any order, over any length of time, which is effective, *e.g.*, simultaneously, consecutively, or alternately. In one embodiment, the method of treatment comprises completing a first course of treatment with one molecule or other treatment before beginning a second course of treatment. The length of time between the end of the first course of treatment and beginning of the second course of treatment can be any length of time that allows the

total course of therapy to be effective, *e.g.*, seconds, minutes, hours, days, weeks, months, or even years.

[0040] The terms "polypeptide" or "protein" means a macromolecule having the amino acid sequence of a native protein, that is, a protein produced by a naturally-occurring and non-recombinant cell; or it is produced by a genetically-engineered or recombinant cell, and comprise molecules having the amino acid sequence of the native protein, or molecules having one or more deletions from, insertions to, and/or substitutions of the amino acid residues of the native sequence. The term also includes amino acid polymers in which one or more amino acids are chemical analogs of a corresponding naturally-occurring amino acid and polymers. The terms "polypeptide" and "protein" encompass IL-23 antibodies and sequences that have one or more deletions from, additions to, and/or substitutions of the amino acid residues of the antigen binding protein sequence. The term "polypeptide fragment" refers to a polypeptide that has an amino-terminal deletion, a carboxyl-terminal deletion, and/or an internal deletion as compared with the full-length native protein. Such fragments may also contain modified amino acids as compared with the native protein. In certain embodiments, fragments are about five to 500 amino acids long. For example, fragments may be at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 50, 70, 100, 110, 150, 200, 250, 300, 350, 400, or 450 amino acids long. Useful polypeptide fragments include immunologically functional fragments of antibodies, including binding domains. In the case of an anti-IL-23 antibody, useful fragments include but are not limited to one or more CDR regions, a variable domain of a heavy or light chain, a portion of an antibody chain, a portion of a variable region including less than three CDRs, and the like.

[0041] The term "isolated protein" refers to a protein, such as an antigen binding protein (an example of which could be an antibody), that is purified from proteins or polypeptides or other contaminants that would interfere with its therapeutic, diagnostic, prophylactic, research or other use. As used herein, "substantially pure" means that the described species of molecule is the predominant species present, that is, on a molar basis it is more abundant than any other individual species in the same mixture. In certain embodiments, a substantially pure molecule is a composition wherein the object species comprises at least 50% (on a molar basis) of all macromolecular species present. In other embodiments, a substantially pure composition will comprise at least 80%, 85%, 90%, 95%, or 99% of all macromolecular species present in the composition. In certain embodiments, an essentially homogeneous substance has been purified to such a degree that contaminating species cannot be

detected in the composition by conventional detection methods and thus the composition consists of a single detectable macromolecular species.

[0042] A "variant" of a polypeptide (e.g., an antigen binding protein such as an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Variants include fusion proteins. A "derivative" of a polypeptide is a polypeptide that has been chemically modified in some manner distinct from insertion, deletion, or substitution variants, e.g., via conjugation to another chemical moiety.

[0043] The terms "naturally occurring" or "native" as used throughout the specification in connection with biological materials such as polypeptides, nucleic acids, host cells, and the like, refers to materials which are found in nature, such as native human IL-23. In certain aspects, recombinant antigen binding proteins that bind native IL-23 are provided. In this context, a "recombinant protein" is a protein made using recombinant techniques, i.e., through the expression of a recombinant nucleic acid as described herein. Methods and techniques for the production of recombinant proteins are well known in the art.

[0044] The term "antibody" refers to an intact immunoglobulin of any isotype, or a fragment thereof that can compete with the intact antibody for specific binding to the target antigen, and includes, for instance, chimeric, humanized, fully human, and bispecific antibodies. An antibody as such is a species of an antigen binding protein. Unless otherwise indicated, the term "antibody" includes, in addition to antibodies comprising two full-length heavy chains and two full-length light chains, derivatives, variants, fragments, and muteins thereof, examples of which are described below. An intact antibody generally will comprise at least two full-length heavy chains and two full-length light chains, but in some instances may include fewer chains such as antibodies naturally occurring in camelids which may comprise only heavy chains. Antibodies may be derived solely from a single source, or may be "chimeric," that is, different portions of the antibody may be derived from two different antibodies as described further below. The antigen binding proteins, antibodies, or binding fragments may be produced in hybridomas, by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact antibodies.

[0045] The term "functional fragment" (or simply "fragment") of an antibody or immunoglobulin chain (heavy or light chain), as used herein, is an antigen binding protein comprising a portion (regardless of how that portion is obtained or synthesized) of an antibody that lacks at least some of the

amino acids present in a full-length chain but which is capable of specifically binding to an antigen. Such fragments are biologically active in that they bind specifically to the target antigen and can compete with other antigen binding proteins, including intact antibodies, for specific binding to a given epitope. In one aspect, such a fragment will retain at least one CDR present in the full-length light or heavy chain, and in some embodiments will comprise a single heavy chain and/or light chain or portion thereof. These biologically active fragments may be produced by recombinant DNA techniques, or may be produced by enzymatic or chemical cleavage of antigen binding proteins, including intact antibodies. Fragments include, but are not limited to, immunologically functional fragments such as Fab, Fab', F(ab')2, Fv, domain antibodies and single-chain antibodies, and may be derived from any mammalian source, including but not limited to human, mouse, rat, camelid or rabbit. It is contemplated further that a functional portion of the antigen binding proteins disclosed herein, for example, one or more CDRs, could be covalently bound to a second protein or to a small molecule to create a therapeutic agent directed to a particular target in the body, possessing bifunctional therapeutic properties, or having a prolonged serum half-life.

[0046] An "antigen binding protein" as used herein means a protein that specifically binds a specified target antigen; the antigen as provided herein is IL-23, particularly human IL-23, including native human IL-23. Antigen binding proteins as provided herein interact with at least a portion of the unique p19 subunit of IL-23, detectably binding IL-23; but do not bind with any significance to IL-12 (e.g., the p40 and/or the p35 subunits of IL-12), thus "sparing IL-12". As a consequence, the antigen binding proteins provided herein are capable of impacting IL-23 activity without the potential risks that inhibition of IL-12 or the shared p40 subunit might incur. The antigen binding proteins may impact the ability of IL-23 to interact with its receptor, for example by impacting binding to the receptor, such as by interfering with receptor association. In particular, such antigen binding proteins totally or partially reduce, inhibit, interfere with or modulate one or more biological activities of IL-23. Such inhibition or neutralization disrupts a biological response in the presence of the antigen binding protein compared to the response in the absence of the antigen binding protein and can be determined using assays known in the art and described herein. Antigen binding proteins provided herein inhibit IL-23-induced proinflammatory cytokine production, for example IL-23-induced IL-22 production in whole blood cells and IL-23-induced IFNγ expression in NK and whole blood cells. Reduction of biological activity can be about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%,95%, 96%, 97% 98%, 99% or more.

[0047] Certain antigen binding proteins described herein are antibodies, or are derived from antibodies. Such antigen binding proteins include, but are not limited to, monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies, antibody mimetics, chimeric antibodies, humanized antibodies, human antibodies, antibody fusions, antibody conjugates, single chain antibodies, and fragments thereof, respectively. In some instances, the antigen binding protein is an immunological fragment of an antibody (e.g., a Fab, a Fab', a F(ab')2, or a scFv).

[0048] Certain antigen binding proteins that are provided may comprise one or more CDRs as described herein (e.g., 1, 2, 3, 4, 5, 6 or more CDRs). In some instances, the antigen binding protein comprises (a) a polypeptide structure and (b) one or more CDRs that are inserted into and/or joined to the polypeptide structure. The polypeptide structure can take a variety of different forms. For example, it can be, or comprise, the framework of a naturally occurring antibody, or fragment or variant thereof, or may be completely synthetic in nature. Examples of various polypeptide structures are further described below.

[0049] An antigen binding protein of the invention is said to "specifically bind" its target antigen when the dissociation equilibrium constant (KD) is $\leq 10^{-8}$ M. The antigen binding protein specifically binds antigen with "high affinity" when the KD is $\leq 5 \times 10^{-9}$ M, and with "very high affinity" when the the KD is $\leq 5 \times 10^{-10}$ M. In one embodiment the antigen binding protein will bind to human IL-23 with a KD of $\leq 5 \times 10^{-12}$ M, and in yet another embodiment it will bind with a KD $\leq 5 \times 10^{-13}$ M. In another embodiment of the invention, the antigen binding protein has a KD of $\leq 5 \times 10^{-12}$ M and an Koff of about $\leq 5 \times 10^{-6}$ 1/s. In another embodiment, the Koff is $\leq 5 \times 10^{-7}$ 1/s.

[0050] In embodiments where the antigen binding protein is used for therapeutic applications, an antigen binding protein can reduce, inhibit, interfere with or modulate one or more biological activities of IL-23, such inducing production of proinflammatory cytokines. IL-23 has many distinct biological effects, which can be measured in many different assays in different cell types; examples of such assays and known see for example US Patent Application No: US 2013-0004501, the disclosure of which is incorporated by reference herein Exemplary IL-23 antibodies are disclosed US Patent Application No: US 2013-0004501.

[0051] As used herein, "AMG 139" refers to an intact AMG 139 immunoglobulin or to an antigen binding portion thereof that competes with the intact antibody for specific binding, unless otherwise specified. AMG 139 also includes antibodies (or fragments thereof) that are identical or similar to AMG 139 in amino acid sequence, particularly in the variable regions, or in the CDRs thereof

(however, variations in the constant regions are also contemplated). For example, a useful AMG 139 polypeptide has an amino acid sequence that is 85%, 90%, 92%, 95%, 98%, 99% or 100% identical to that of an AMG 139 polypeptide disclosed herein. In another embodiment, a useful polypeptide is between 80% and 100% identical to AMG 139.

[0052] AMG139 is a human antibody that specifically recognizes the native human IL-23 heterodimer, but does not bind with any significance to the human IL-12 heterodimer. AMG139 inhibits IL-23-induced proinflammatory cytokine production, for example IL-23-induced IL-22 production in whole blood cells and IL-23-induced IFNγ expression in NK and whole blood cells. In some embodiments, AMG 139 is an isolated, IL-23 specific antigen binding protein having a heavy chain variable region comprising CDR1, CDR2 and CDR3 from SEQ ID NO:1, and a light chain variable region comprising CDR1, CDR2 and CDR3 from SEQ ID NO:2. In some embodiments, AMG 139 is an isolated, IL-23 specific antigen binding protein wherein the heavy chain variable region is at least 90% identical to SEQ ID NO:1, and the light chain variable region is at least 90% identical to CDR1, CDR2 and CDR3 from SEQ ID NO:2. See, WO 2011/056600 published May 11, 2011.

[0053] Where a range of values is provided, it is understood that each intervening value (to the tenth of the unit of the lower limit unless the context clearly dictates otherwise) between the upper and lower limit of that range, and any other stated or intervening value or smaller range, in that stated range is encompassed within the invention. The upper and lower limits of smaller ranges may independently be included in the smaller range, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

[0054] Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification

unless otherwise indicated. See, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001) and Ausubel et al., Current Protocols in Molecular Biology, Greene Publishing Associates (1992), and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The terminology used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[0055] All patents and other publications identified are expressly incorporated herein by reference in their entirety for the purpose of describing and disclosing, for example, the methodologies described in such publications that might be used in connection with information described herein.

[0056] The following examples, both actual and prophetic, are provided for the purpose of illustrating specific embodiments or features of the instant invention and do not limit its scope.

Example 1

[0057] This example describes a Phase 1, randomized, double-blind, placebo-controlled, ascending single dose study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of an anti-IL-23 antibody (AMG 139) in healthy subjects (HS) and subjects with moderate to severe psoriasis (PSO); ClinicalTrials.gov Identifier: NCT01094093).

[0058] A total of 73 subjects were randomized into the study; 56 healthy adults were randomized in Part A and received AMG 139 as a single SC dose (7, 21, 70, or 210 mg) or single IV dose (210, 420, or 700 mg) or placebo, and 17 subjects with moderate to severe PsO were randomized in Part B and received AMG 139 as a single SC dose (21, 70, or 210 mg) or single IV dose (700 mg) or placebo, see Table 1.

Table 1. Dosage and Administration Route for Each Cohort

Cohorts	Dosage (mg)	Route	Number of Subjects (AMG 139:placebo)
PART A	Healthy Subjects (HS)		

Cohort A1	7	SC	2 (1:1) 6 (5:1)
Cohort A2	21	SC	8 (6:2)
Cohort A3	70	SC	8 (6:2)
Cohort A4	210	SC	8 (6:2)
Cohort A5	210	IV	8 (6:2)
Cohort A6	420	IV	8 (6:2)
Cohort A7	700	IV	8 (6:2)
PART B	Subjects with PsO		
Cohort B1	21	SC	4 (3:1)
Cohort B2	70	SC	4 (3:1)
Cohort B3	210	SC	4 (3:1)
Cohort B4	700	IV	4 (3:1)

[0059] Serial blood samples were taken at scheduled time points in Part A to day 85 for cohorts A1, A2 and A3 and day 169 for cohorts A5, A6 and A7. For Part B, scheduled time points were to day 113 for cohorts B1 and B2 (21 and 70 mg AMG139 SC, respectfully). Day 169 for cohorts B3 and B4 (210 SC and 700IV AMG139, respectfully).

[0060] To measure the amount of AMG 139 in serum from a subject, capture antibody (mouse anti-AMG 139 1F2 mAb) was passively adsorbed to Multi-Array® 96-well HighBind microplate wells (Meso Scale Discovery). The microplate wells were blocked with Blocker™ BLOTTO buffer after removing excess capture antibody. Standards and quality control samples, prepared by spiking known quantities of AMG 139 into 100% normal human serum pool, were loaded into the microplate wells after pre-treating with a dilution factor of 100 in Blocker™ BLOTTO buffer, as are samples to be tested and matrix blank. Any AMG 139 in the samples was captured by the immobilized capture antibody. Unbound material was removed by washing the microplate wells. Following washing, SULFO-TAGTM conjugated detection antibody (anti-AMG 139 1A4.1 mAb) was added to the microplate wells to bind captured AMG 139. Unbound SULFO-TAGTM conjugated capture antibody was removed by washing the microplate wells.

[0061] Following this washing, Read Buffer T (Meso Scale Discovery) was added to aid in the detection of bound SULFO-TAGTM conjugated detection antibody. When the microplate is electrically stimulated, the SULFO-TAGTM label, in the presence of the co-reactant tripropylamine

(TPA) in the read buffer, emits light at 620 nm. The quantity of light emitted is proportional to the amount of AMG 139 bound by the capture antibody in the initial step. Light emission was detected using an appropriate plate reader; for example, a Sector Imager 6000 equipped with Discovery Workbench software. Data were reduced using Watson Laboratory Information Management System data reduction package using a 5PL (autoestimate) (5-parameter logistic) regression model with a weighting factor of 1/Y2. The amount of AMG 139 in a given serum sample was determined by comparison to the standard curve formed by the standards and quality control samples.

[0062] In Part A, the AMG 139 serum concentration versus time profiles for healthy subjects (n = 42) exhibited linear PK, as indicated by serum AMG 139 exposure that increased approximately dose proportionally across all doses tested, except for the 7 mg SC dose (Figures 1 and 2). The median T_{max} values across doses ranged from 4 to 8 days after a single SC administration (Table 2). Relative bioavailability after a single SC dose was estimated to be 68.9%. Group mean estimates of the terminal half-life after SC or IV administration across all dose levels ranged from 26.6 to 33.0 days, which are typical of an IgG antibody.

[0063] In Part B, the AMG 139 serum concentration versus time profiles for subjects with PsO (n = 12) exhibited linear PK, as indicated by serum AMG 139 exposure that increased approximately dose proportionally across all doses tested in this study (Figures 3 and 4). The median T_{max} values across doses ranged from 9 to 13 days after a single SC administration (Table 1). Relative bioavailability after a single SC or IV dose was estimated to be 66.9%. Group mean estimates of the terminal half-life after SC or IV administration across all dose levels ranged from 21.6 to 31.0 days, which are typical of an IgG antibody.

[0064] In general, AMG 139 PK was similar between healthy subjects in Part A and subjects with PsO in Part B. The one exception was that healthy subjects showed greater exposure (AUC and C_{max}) of AMG 139 compared to the subjects with PsO. The median T_{max} after SC administration occurred earlier for healthy subjects than for subjects with PsO. Mean half-life values of AMG 139 were similar between healthy subjects (26.6 to 33.0 days) and subjects with PsO (21.6 to 31.0 days), as were bioavailabilities (68.9% and 66.9%, respectively). Clearance (CL) and volume of distribution (V_z) of AMG 139 were consistent across dose levels among healthy subjects (Part A) and among subjects with PsO (Part B).

[0065] Patient samples were also tested for binding antibodies to AMG 139. The assay utilized a electrochemiluminescence (ECL) MSD (Meso Scale Discovery) technology platform, which is based

on multivalent characteristics of antibody binding. The testing strategy involved a tiered two-assay approach consisting of a screening assay and a specificity assay. Samples with signal to noise ratio (S/N) greater than assay cut point in the screening assay were further tested in the specificity assay by incubating the sample with excess AMG 139 prior to testing.

[0066] To enable dissociation of antibody complexes, acid treatment of samples was performed prior to analysis. Acid-treated serum samples and controls were added to a solution consisting of equal parts of biotinylated-AMG 139 (B-AMG 139) and ruthenylated-AMG 139 (Ru-AMG 139) in 1 M Tris, pH 9.5, and are incubated at ambient temperature to allow for anti-AMG 139 antibodies to bind both a B-AMG 139 molecule and a Ru-AMG 139 molecule, thereby forming a complex.

[0067] Following the incubation, all samples and controls are transferred to a washed streptavidin-coated standard bind MSD plate blocked with bovine serum albumin and incubated at ambient temperature to allow for the capture of B-AMG 139 and formed complexes on the streptavidin surface. The plate wells are washed and a solution of MSD read buffer containing tripropylamine is added. The plate is read on the MSD Sector Imager 6000 plate reader. Within the instrument, ruthenium participates in an electrochemiluminescent reaction that is triggered when the voltage was applied. The complexes containing the Ru-AMG 139 that are captured on the wells of the plate result in an ECL signal proportionate to the concentration of anti-AMG 139 antibodies in the sample.

[0068] None of the 73 subjects in this study developed anti-drug antibodies. Therefore, the potential effects of immunogenicity on AMG 139 disposition could not be assessed.

Table 2: Mean PK Parameters of AMG 139 After Single-dose SC or IV Administration in Healthy Subjects (Part A) and Subjects with PsO (Part B), Study 20080767

Route	Dose (mg)	N	C_{max} (µg/mL)	t_{max} (day)	AUC_{last} (day•µg/mL)	AUC_{inf} (day•µg/mL)	$t_{1/2,z}$ (day)	CL^a (mL/day)	V_Z^a (L)
Part A (Healthy Subjects)									
SC	7	6	0.581(20.0)	6.0(1.0-21)	26.4(28.2)	28.9(29.6)	30.3(13.0)	256(22.9)	11.1(22.1)
	21	6	1.72(33.7)	8.0(4.0-14)	71.7(17.3)	76.2(16.5)	26.6(11.3)	282(15.9)	10.8(21.0)
	70	6	7.79(23.4)	8.0(7.8-8.2)	341(32.9)	373(35.2)	29.0(21.0)	218(51.3)	8.34(20.5)
	210	6	24.3(22.2)	4.0(3.9-10)	940(28.9)	1008(27.6)	27.8(12.3)	223(30.0)	8.83(26.3)
IV	210	6	73.0(20.4)	0.17(0.17-0.33)	1430(22.7)	1471(20.8)	28.4(11.1)	147(18.0)	5.98(15.9)
	420	6	122(14.9)	0.17(0.063-0.17)	2109(24.1)	2453(13.7)	33.0(5.6)	174(13.3)	8.25(11.3)
	700	6	175(16.8)	0.17(0.042-0.33)	3705(17.6)	3801(17.8)	32.9(10.9)	188(15.0)	8.93(18.3)
Part B (Subjects with PsO)									

SC	21	3	1.23(18.1)	13(6.0-13)	62.2(4.5)	67.8(4.9)	29.9(10.6)	310(4.8)	13.4(9.8)
	70	3	5.43(21.6)	10(6.0-10)	200(38.6)	207(40.6)	21.6(15.6)	376(38.0)	11.4(29.1)
	210	3	13.7(14.5)	9.0(4.0-9.9)	630(20.2)	637(20.3)	25.6(11.3)	338(18.2)	12.4(19.2)
IV	700	3	157(17.6)	0.17(0.057-0.33)	3101(17.6)	3138(18.0)	31.0(8.1)	229(20.1)	10.2(16.2)

AUC_{inf} = area under the concentration-time curve from time 0 to infinity; AUC_{last} = area under the concentration-time curve from time 0 to the time of the last measurable concentration; CL = clearance; C_{max} = maximum observed concentration post dose; %CV = coefficient of variation; F = bioavailability; IV = intravenous(ly); PsO = psoriasis; SC = subcutaneous(ly); $t_{1/2,z}$ = elimination half-life; t_{max} = time to maximum observed concentration; V_z = volume of distribution; V_z/F = apparent volume of distribution

PK parameters are reported as mean (CV%) with 3 significant figures except for t_{max} which is reported as median(min-max) rounded to 2 significant figures. %CV is reported to 1 decimal place.

[a] CL and V_z represent CL/F and V_z/F for SC administration.

Example 2

[0069] The efficacy of AMG 139 was evaluated in subjects with PsO as a secondary endpoint in the previously mentioned Phase 1a FIH study (20080767, Part B). Reductions in mean Psoriasis Area and Severity Index (PASI) scores (Figures 5 and 6, and Table 3), mean target lesion scores, and mean Physician Global Assessments (PGAs) occurred in all AMG 139 treatment groups compared with the placebo group. Even though the numbers of subjects per treatment group were small, it was clearly apparent that the single administrations of AMG 139 were efficacious with respect to degree and duration of responses in treatment groups receiving doses as low as 70 mg SC. Efficacy was also apparent from the number and percent of subjects reaching PASI 50, PASI 75, or PASI 90 over time by treatment group, and from the number and percent of subjects reaching PASI 50, PASI 75, PASI 90, or PASI 100 at any time during the study by treatment group. For any given dose, treatment effects (PASI, target lesion score, PGA) appeared to reach their maximum by approximately Day 85 to Day 113. Mean percent changes from baseline in PASI score was as high as approximately 90% (i.e., at Days 85, 113, and 169 in the AMG 139 210 mg SC group). Results past Day 113 for the AMG 139 210 mg SC and 700 mg IV groups suggested that AMG 139 treatment effects from the single doses began to return toward baseline after approximately Day 169. With group-mean terminal half-life values for AMG 139 mostly being in the range of 25 to 30 days, circulating levels of AMG 139 by Day 169 were approximately 1% to 2% of C_{max} for any given dose. Photographs of subjects and subject lesions were also taken at various time points. Overall, these photographs were visually and qualitatively consistent with the PASI, target lesion assessment, and PGA results.

Table 3: Summary of Subjects Reaching PASI 50, PASI 75, PASI 90, or PASI 100 at Any Time During the Study (Part B: Study 20080767)

PASI Response	Treatment Group				
	Placebo Part B N = 5 n (%)	Cohort B1 21 mg SC N = 3 n (%)	Cohort B2 70 mg SC N = 3 n (%)	Cohort B3 210 mg SC N = 3 n (%)	Cohort B4 700 mg IV N = 3 n (%)
PASI 50	2 (40)	3 (100)	3 (100)	3 (100)	3 (100)
PASI 75	0 (0)	1 (33)	3 (100)	3 (100)	2 (67)
PASI 90	0 (0)	1 (33)	1 (33)	2 (67)	1 (33)
PASI 100	0 (0)	0 (0)	0 (0)	2 (67)	0 (0)

IV = intravenous; N = number of subjects with PASI score at baseline; PASI = Psoriasis Activity and Severity Index; SC = subcutaneous

Example 3

[0070] A quantitative population pharmacokinetics (pop PK) model for AMG 139 was established to simulate the PK of future dosing regimens, as well as incorporation with a quantitative PK/pharmacodynamic model for simulating AMG 139 efficacy. The pop PK model was based on healthy subject and PsO patient data described above.

[0071] Pop PK modeling of subcutaneous (SC; 7, 21, 70, or 210 mg) or intravenous (IV; 210, 420, or 700 mg) doses was performed with NONMEM v7.2. Data analysis used individual PK data fit simultaneously to a structural two-compartment model with first-order elimination from the central compartment and first-order absorption from a depot compartment (Figure 7). The inter-subject variability parameters and residual error model were varied to obtain the lowest objective function. Body weight and disease were explored as potential PK covariates.

[0072] The final AMG 139 pop PK model predicted mean concentration-time profiles that fit the data well within 90% confidence intervals (Figure 8), and visual predictive diagnostic plots show strong correlations between observed and predicted values (Figures 8 and 9). Absorption rate constant, systemic clearance (CL), and central volume of distribution (V_c) were 0.242 h^{-1}, 0.171 L/day, and 3.58 L, respectively, with inter-individual variability of 66%, 24%, and 20%, respectively (Table 4). Body weight as a covariate had power coefficient values of 1.04 and 1.11 for CL and V_c, respectively, and showed a positive correlation with CL and V_c (Figure 10). After adjusting for body weight, the

additional effect of a disease status covariate on CL [1.13-fold increase (0.93-1.3, 95% CI)] did not show a statistically significant improvement on the model in this Phase 1 study dataset.

Table 4: Population PK Model Parameter Estimates after Single Dose Administration of AMG 139 to Healthy Volunteers and Psoriasis Subjects

Parameter	Parameter estimate	SE	Inter-individual variability (%)	SE
ka (hr^{-1})	0.242	0.0354	66	9
CL (L/day)	0.171	0.0149	24	3
V_c (L)	3.58	0.318	20	2
V_p (L)	3.16	0.322	25	3
Q (L)	0.576	0.107	90	15

[0073] The AMG 139 pop PK model established utility for simulating AMG 139 PK in future inflammatory disease populations, as well as incorporation with ongoing efficacy studies for establishment of a PK/pharmacodynamic model.

[0074] These results support several dosing regimens for administering an anti-IL-23 antibody to an individual afflicted with a psoriatic condition that is associated with the IL-23 pathway. An appropriate dosing regimen can be selected from the dosing regimens shown in Table 5 below.

Table 5: Dosing Regimens

21 mg SC or IV every 1 month (0.5 – 1.5 months); 21 mg includes amounts in the range of 15 – 54 mg
70 mg SC or IV every 3 months (1.5 – 4.5 months); 70 mg includes amounts in the range of 55 – 149 mg
210 mg SC or IV every 6 months (4 – 8 months); 210 mg includes amounts in the range of 150 – 299 mg
700 mg SC or IV every 6 months (4 – 12 months); 700 mg includes amounts in the range of 300 – 1100 mg

Example 4

[0075] Immunophenotyping was a primary endpoint in Part A and B of this study. Lymphocyte populations including T cells, B cells, NK cells, regulatory T cells (Tregs), and Th17 cells were quantified over time by flow cytometry performed on whole blood samples.

[0076] Whole blood was collected from subjects at indicated time points in potassium EDTA (ethylenediaminetetraacetic acid)-containing glass tubes and processed within 24 hours (Cohorts A1-A7) or following a 24 hour incubation period at room temperature (Cohorts B1-B4). The CYTO-STAT tetraCHROME® staining kit (Beckman Coulter, Fullerton, CA) was used for enumeration of T (CD3+, CD4+ and CD8+), B and NK cell populations. Other T cell populations (Treg and Th17 cells) were identified in separate tubes using custom combinations of fluorochrome-conjugated monoclonal antibodies.

[0077] After antibody staining of whole blood, red blood cells were lysed in all samples using Coulter IMMUNOPREP reagent system (Beckman Coulter) and fixed in a 1% solution of paraformaldehyde. For blood stained with markers for T, B, and NK cells, samples were then immediately analyzed by flow cytometry. Blood stained with markers for Treg and Th17 cell populations was washed prior to analysis by flow cytometry.

Flow cytometry

[0078] Data acquisition and analysis was performed using a FC500 flow cytometer (Beckman Coulter) with a single blue laser (488 nm) and a 5-color optical configuration. An initial lymphocyte gate was set on the CD45-expressing population exhibiting low side scatter characteristics. T cell

(including Treg and Th17) and NK T cell populations were derived from the CD3+ subset of lymphocytes. NK and B cell populations were identified from the non-CD3 expressing subset of lymphoctyes.

[0079] The CYTO-STAT tetraCHROME® staining kit (Beckman Coulter) allows for enumeration of T, B, NK and NK T cells using Flow-Count Fluorospheres (Beckman Coulter) using a single platfrom; therefore, these populations are reported as absolute counts. Treg and Th17 cells are reported as percentages of total CD3+ CD4+ cells since Flow-Count Fluorospheres were not included in these tests. Absolute counts for these populations can be calculated using the clinical lymphocyte counts from each enrolled subject on the day of immunophenotypic analysis.

[0080] No directional changes in quantities of the above-mentioned types of lymphocytes or in frequencies of CD4+ or CD8+ lymphocytes expressing the above-mentioned cytokines upon in vitro stimulation were observed in AMG 139-treated subjects. Fewer differentially regulated genes (lesional/nonlesional) were observed after treatment of PsO subjects with AMG 139, consistent with a drug-related PD effect.

Claims

What is claimed is:

1. A method of treating psoriasis in a subject in need thereof comprising administering to the subject an anti-IL-23 antibody in an amount and at an interval of:

a. 15 – 54 mg every 0.5 – 1.5 months;

b. 55 – 149 mg every 1.5 – 4.5 months;

c. 150 – 299 mg every 4 – 8 months; or

d. 300 – 1100 mg every 4 – 12 months.

2. The method of claim 1, wherein the amount and interval are:

a. 15 – 21 mg every 0.5 – 1.0 month;

b. 55 – 70 mg every 1.5 – 3.0months;

c. 150 – 260 mg every 4 – 6 months; or

d. 300 – 700 mg every 4 – 8 months.

3. The method of claim 1, wherein the amount and interval are:

a. 21 mg every month;

b. 70 mg every 3 months;

c. 210mg every 6 months; or

d. 700 mg every 6 months.

4. The method of claim 1, wherein the amount and interval are:

a. 210 mg every 3 months or

b. 700 mg every 3 months.

5. The method of claim 1, wherein the amount and interval are:

a. 210 mg every 1 month or

b. 700 mg every 1 month.

6. A method of treating psoriasis in a subject in need thereof comprising administering to the subject an amount of an anti-IL-23 antibody in an amount and at an interval sufficient to achieve and/or maintain a quantity of anti-IL-23 antibody per volume of serum of between 12.5 ng /ml and 1000 ng/ml.

7. The method of claim 6, wherein the quantity of an anti-IL-23 antibody per volume of serum is at least 10 ng/ml.

8. The method of claim 6, wherein the quantity of an anti-IL-23 antibody per volume of serum is selected from the group consisting of: at least 25 ng/ml; at least 50 ng/ml; at least 60 ng/ml; at least 70 ng/ml; at least 75 ng/ml; and at least 80 ng/ml.

9. The method of claim 6, wherein the quantity of an anti-IL-23 antibody per volume of serum is between 85 ng/ml and 100 ng/ml.

10. The method of claim 6, wherein the quantity of an anti-IL-23 antibody per volume of serum is between 70 ng/ml and 150 ng/ml.

11. The method of claim 6, wherein the quantity of an anti-IL-23 antibody per volume of serum is is between 50 ng/ml and 250 ng/ml.

12. The method of claim 6, wherein the quantity of an anti-IL-23 antibody per volume of serum is is between 40 ng/ml and 500 ng/ml.

13. The method of claim 6, wherein the quantity of an anti-IL-23 antibody per volume of serum is between 25 ng/ml and 750 ng/ml.

14. The method of claim 6, wherein the quantity of an anti-IL-23 antibody per volume of serum is between 10 ng/ml and 1,000 ng/ml.

15. The method according to any of the above claims, wherein the anti-IL23 antibody is administered IV.

16. The method according to any of the above claims, wherein the anti-IL23 antibody is administered SC.

17. The method according to any of the above claims, wherein the anti-IL-23 antibody is AMG 139.

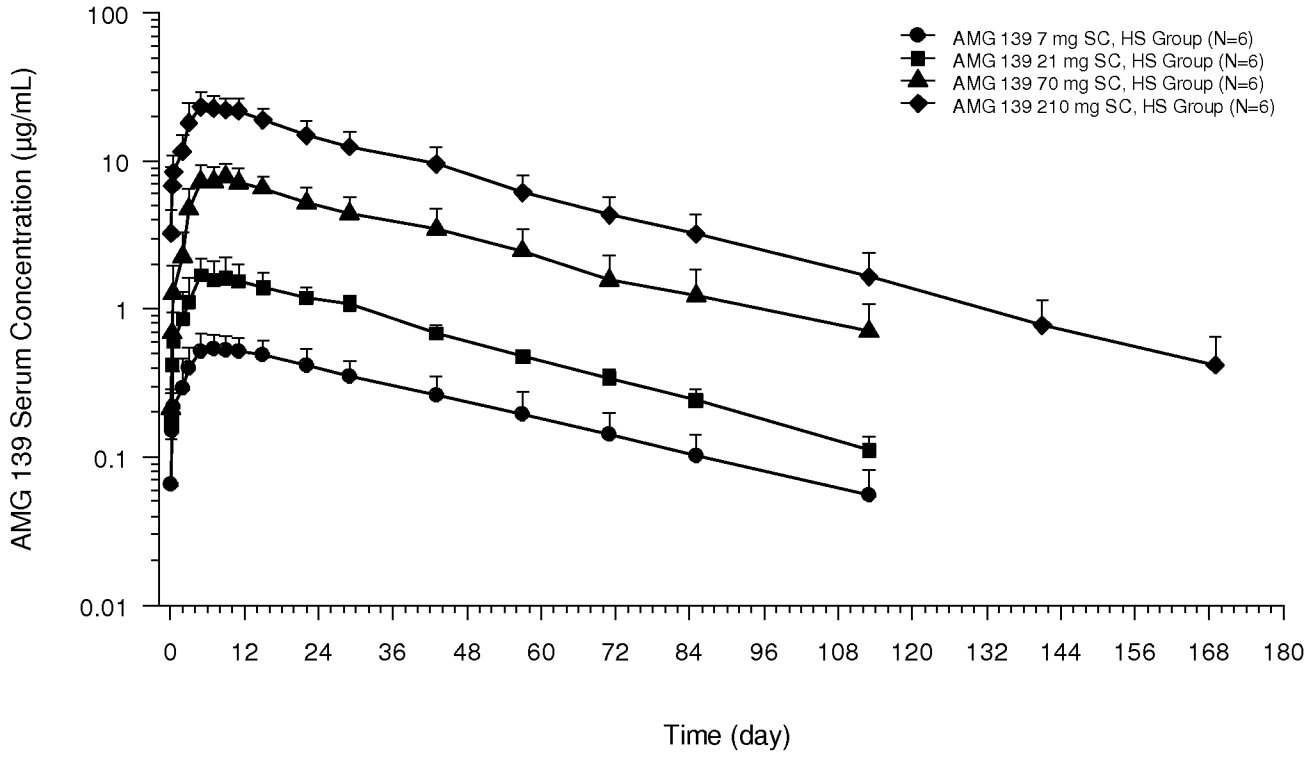
AMG 139 7 mg SC, HS Group (N=6)
AMG 139 21 mg SC, HS Group (N=6)
AMG 139 70 mg SC, HS Group (N=6)
AMG 139 210 mg SC, HS Group (N=6)
AMG 139 Serum Concentration (µg/mL)
100
10
1
0.1
0.01
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
180
Time (day)

Figure 1

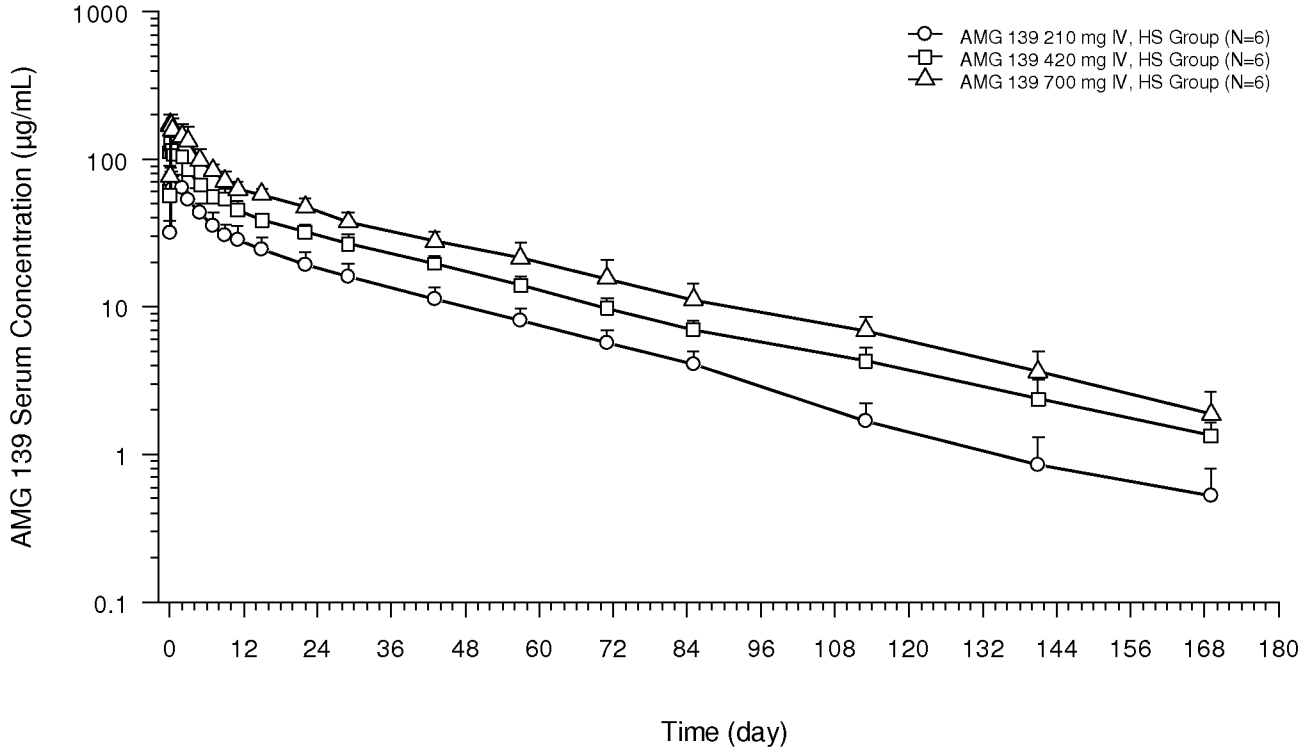
AMG 139 210 mg IV, HS Group (N=6)
AMG 139 420 mg IV, HS Group (N=6)
AMG 139 700 mg IV, HS Group (N=6)
AMG 139 Serum Concentration (µg/mL)
1000
100
10
1
0.1
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
180
Time (day)

Figure 2

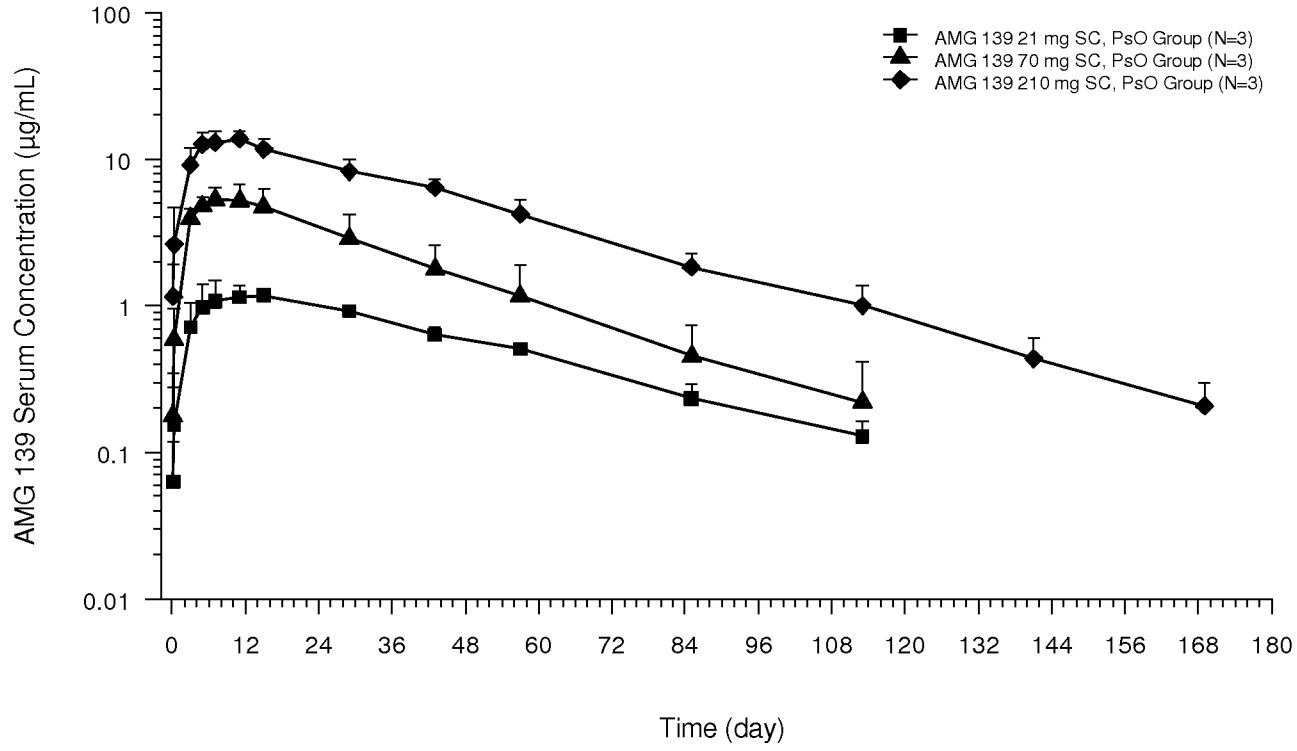
AMG 139 21 mg SC, PsO Group (N=3)
AMG 139 70 mg SC, PsO Group (N=3)
AMG 139 210 mg SC, PsO Group (N=3)
AMG 139 Serum Concentration (µg/mL)
100
10
1
0.1
0.01
0
12
24
36
48
60
72
84
96
108
120
132
144
156
168
180
Time (day)

Figure 3

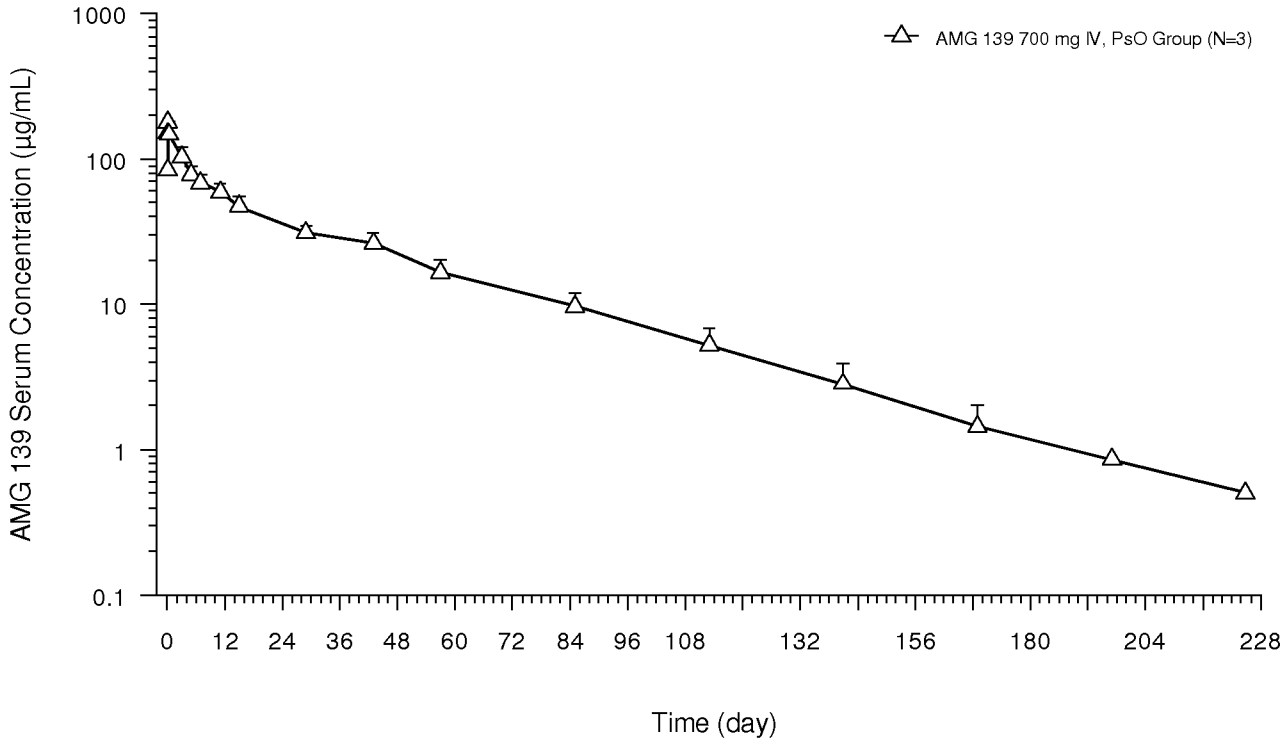
AMG 139 700 mg IV, PsO Group (N=3)
AMG 139 Serum Concentration (µg/mL)
1000
100
10
1
0.1
0
12
24
36
48
60
72
84
96
108
132
156
180
204
228
Time (day)

Figure 4

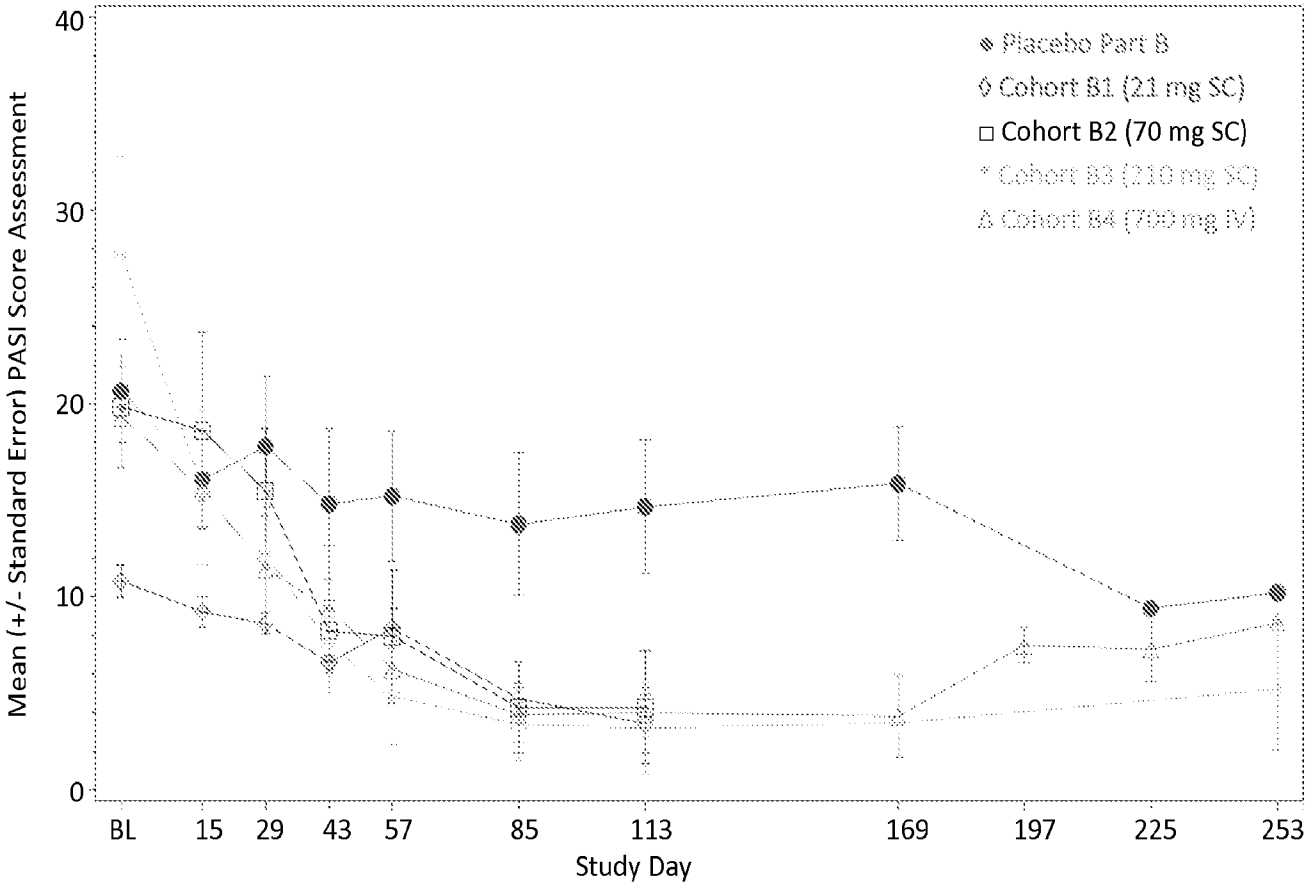
Placebo Part B
Cohort B1 (21 mg SC)
Cohort B2 (70 mg SC)
Cohort B3 (210 mg SC)
Cohort B4 (700 mg IV)
Mean (+/- Standard Error) PASI Score Assessment
40
30
20
10
0
BL
15
29
43
57
85
113
169
197
225
253
Study Day

Figure 5

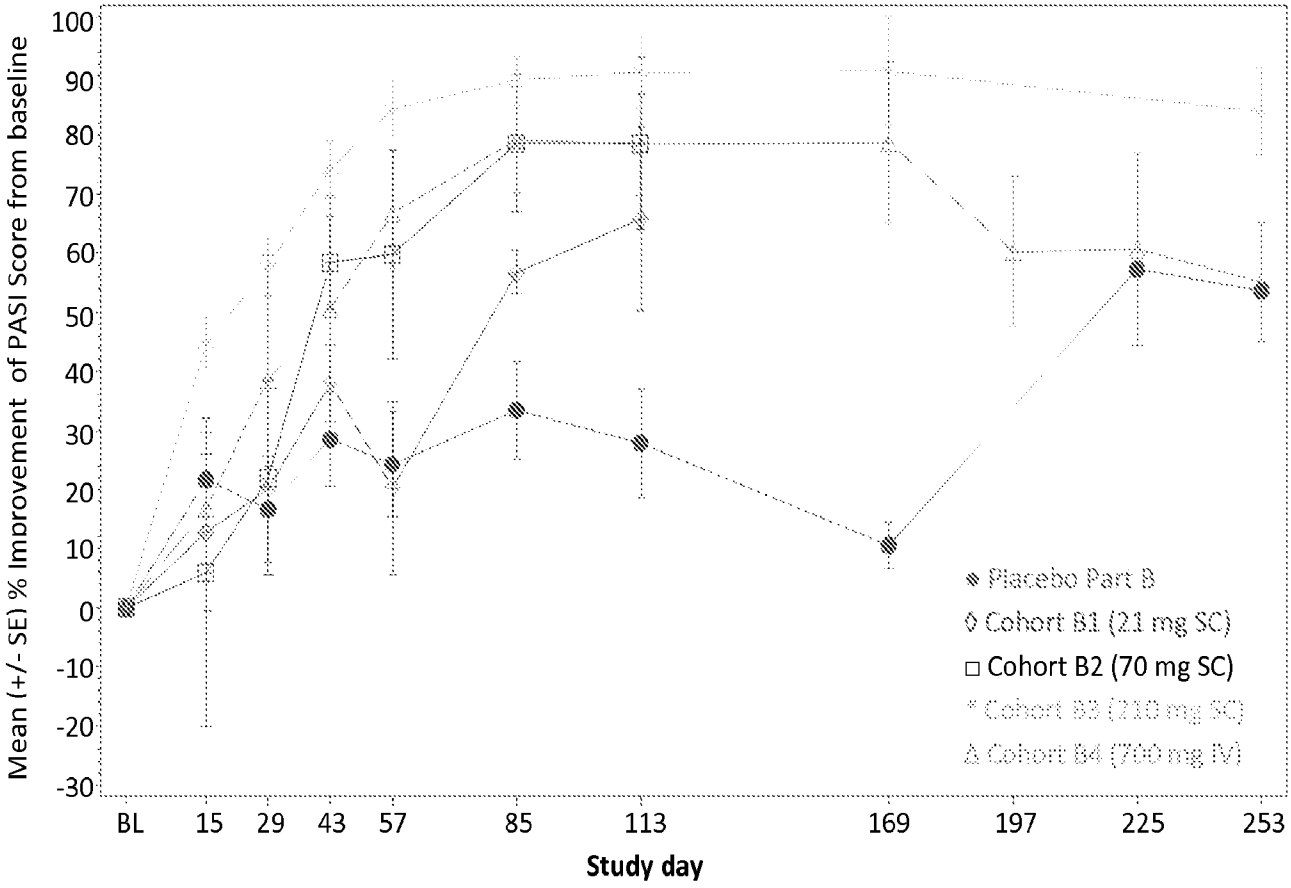
Mean (+/- SE) % Improvement of PASI Score from baseline
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
BL
15
29
43
57
85
113
169
197
225
253
Study day
Placebo Part B
Cohort B1 (21 mg SC)
Cohort B2 (70 mg SC)
Cohort B3 (210 mg SC)
Cohort B4 (700 mg IV)

Figure 6

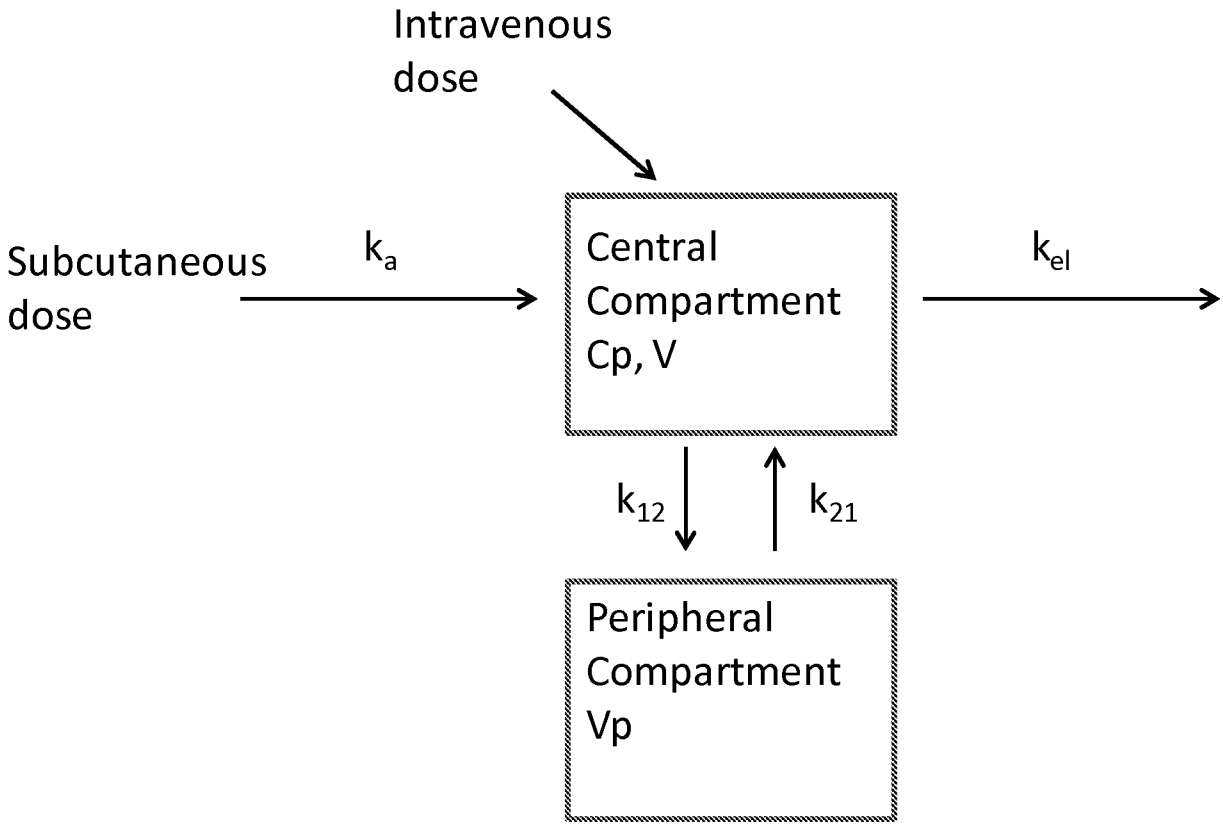
Intravenous dose
Subcutaneous dose
k_a
Central Compartment Cp, V
k_{el}
k_{12}
k_{21}
Peripheral Compartment Vp

Figure 7

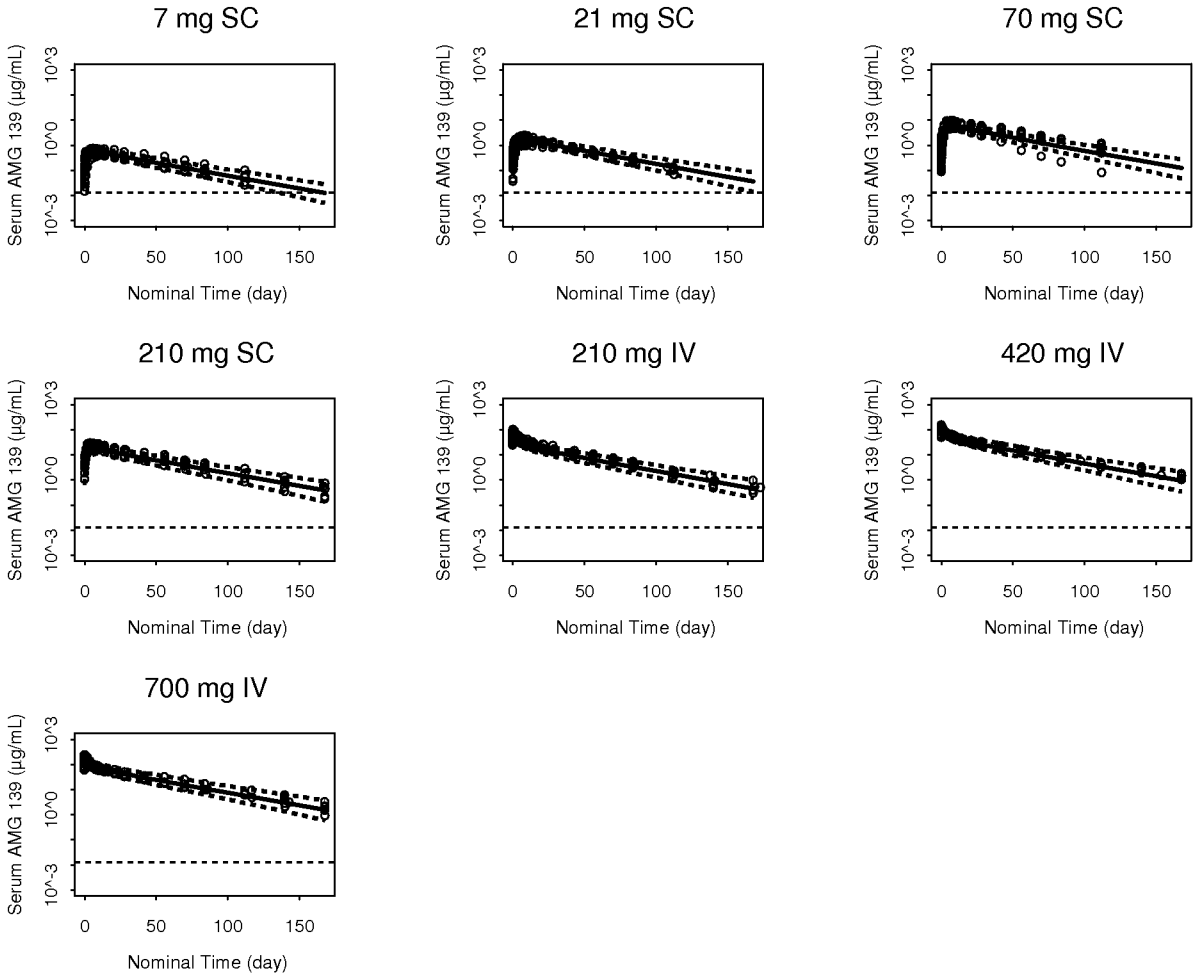
7 mg SC
21 mg SC
70 mg SC
210 mg SC
210 mg IV
420 mg IV
700 mg IV
Serum AMG 139 (µg/mL)
10^3
10^0
10^-3
0
50
100
150
Nominal Time (day)

Figure 8

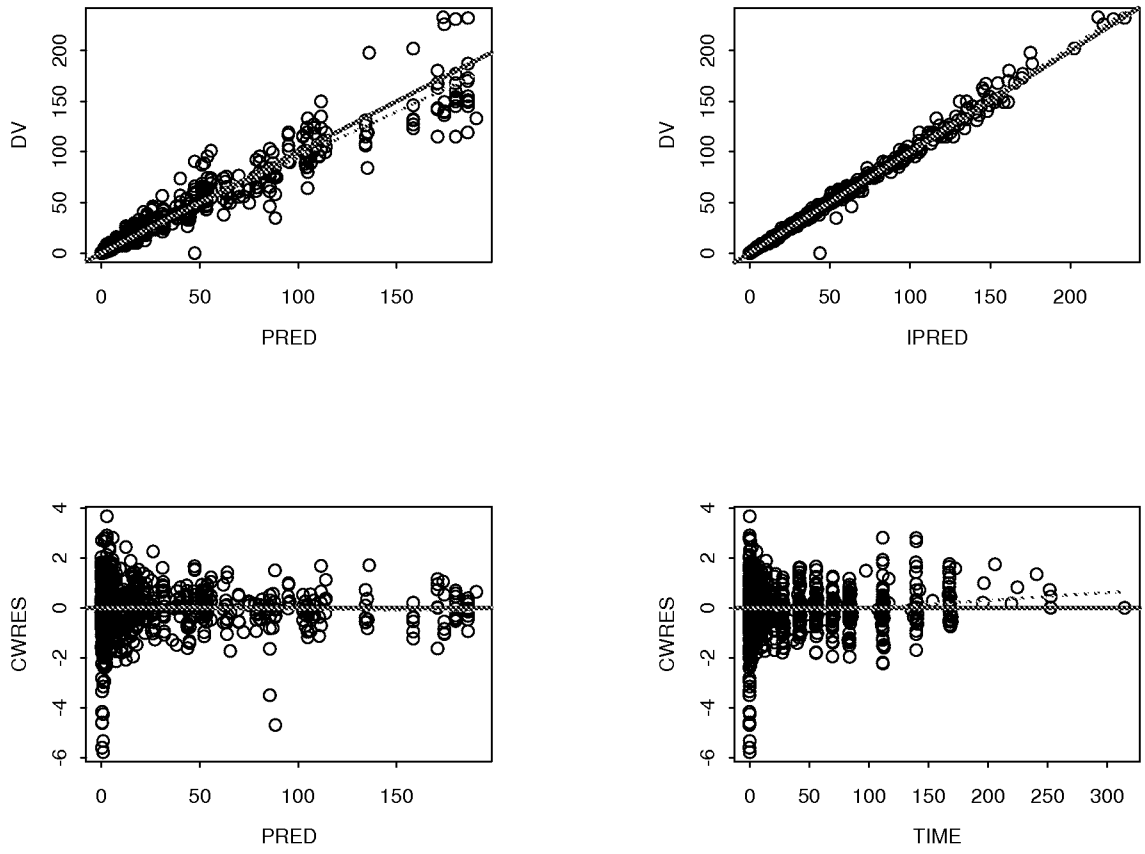

Figure 9

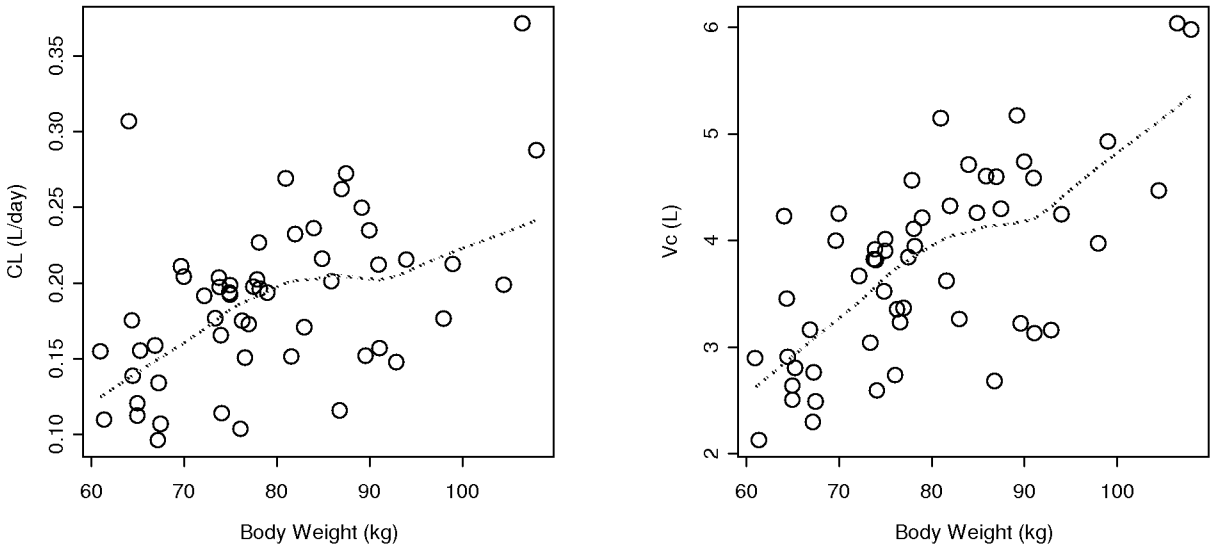
CL (L/day)
0.10
0.15
0.20
0.25
0.30
0.35
60
70
80
90
100
Body Weight (kg)
Vc (L)
2
3
4
5
6
60
70
80
90
100
Body Weight (kg)

Figure 10

V_H1 (SEQ ID NO: 1)

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNEYYADSVKGR
CDR 1 CDR 2

FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGYTSSWYPDAFDIWGQGTMVTVSS
CDR 3

V_L1 (SEQ ID NO: 2)

QSVLTQPPSVSGAPGQRVTISCTGSSSNTGAGYDVHWYQQVPGTAPKLLIYGSGNRPS
CDR 1 CDR 2

GVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSGWVFGGGTRLTVL
CDR 3

Figure 11

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/018293

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/00 A61K39/395 C07K16/24
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/117289 A2 (ABBOTT LAB [US]; VALDES JOAQUIN MARIO [US]; PAULSON SUSAN K [US]) 24 September 2009 (2009-09-24)	1-16
Y	The whole document, but see in particular page 4, lines 1-25; claims 1, 16, and 38; Exampole 7; Figures 6A and 6B.	17

X	WO 2012/048134 A2 (ABBOTT LAB [US]; ABBOTT GMBH & CO KG [DE]; VALDES JOAQUIN MARIO [US];) 12 April 2012 (2012-04-12)	1,6-16
Y	The whole document but see e.g. claims 57-63 and page 116.	1-17

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 April 2014	22/04/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Valcárcel, Rafael

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FOR THE PHOENIX 1 STUDY INVESTIGATORS ET AL: "Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1)", THE LANCET, LANCET LIMITED. LONDON, GB, vol. 371, no. 9625, 17 May 2008 (2008-05-17), pages 1665-1674, XP022666486, ISSN: 0140-6736, DOI: 10.1016/S0140-6736(08)60725-4 [retrieved on 2008-05-15]	1,6-14, 16
Y	The whole document but see e.g. the abstract or page 1667	1-17

X	FOR THE PHOENIX 2 STUDY INVESTIGATORS ET AL: "Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2)", THE LANCET, LANCET LIMITED. LONDON, GB, vol. 371, no. 9625, 17 May 2008 (2008-05-17), pages 1675-1684, XP022683389, ISSN: 0140-6736, DOI: 10.1016/S0140-6736(08)60726-6 [retrieved on 2008-05-17]	1,6-14, 16
Y	The whole document, but see e.g. the abstract or page 1676	1-17

X	DUVALLET EMILIE ET AL: "Interleukin-23: A key cytokine in inflammatory diseases", ANNALS OF MEDICINE, TAYLOR & FRANCIS A B, SE, vol. 43, no. 7, 1 November 2011 (2011-11-01), pages 503-511, XP009177356, ISSN: 0785-3890, DOI: 10.3109/07853890.2011.577093	1-17
Y	The whole document but see e.g. the abstract	1-17

	-/--	

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/056600 A1 (AMGEN INC [US]; TOWNE JENNIFER E [US]; CHENG JANET D [US]; O'NEILL JAS) 12 May 2011 (2011-05-12)	1,6-17
Y	The whole document, but see e.g. the following sections. SEQ ID NO: 31 of this document (referred to as D6) is identical to SEQ ID NO: 1 of the present application (said sequence corresponds to the VH of the antibody arbitrarily designated AMG139 in the present application). SEQ ID NO: 1 of D6 is identical to SEQ ID NO: 2 of the present application (said sequence corresponds to the VL of the antibody arbitrarily designated AMG139 in the present application). D6 discloses the use of this antibody to treat or prevent psoriasis (see e.g. claim 66; page 8, line 35; page 45, lines 24 and 25; or page 49, lines 25-27). For the dosage regimens see pages 48 and 49.	1-17

X	WO 2008/103473 A1 (SCHERING CORP [US]; PRESTA LEONARD G [US]; BEYER BRIAN M [US]; INGRAM) 28 August 2008 (2008-08-28)	1,6-16
Y	See e.g. claims 26 and 51 or paragraphs that refer to the treatment of psoriasis with anti-IL-23 p19 antibodies ([0030], [0033], [0034], [0087] or[0154]) or paragraph [0140] for the different dosages.	1-17

Y	WO 2012/045848 A1 (NOVARTIS AG [CH]; GUETTNER ACHIM [CH]; MACHACEK MATTHIAS [CH]; PAPAVAS) 12 April 2012 (2012-04-12) See e.g. page 56, second paragraph; where the combination of an anti-IL-17 antibody and AMG 139 in the treatment of psoriasis is disclosed.	1-17

Y	TORTI ET AL: "Interleukin-12, interleukin-23, and psoriasis: Current prospects", JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, MOSBY, INC, US, vol. 57, no. 6, 14 November 2007 (2007-11-14), pages 1059-1068, XP022341149, ISSN: 0190-9622, DOI: 10.1016/J.JAAD.2007.07.016 the whole document	1-17

Y	WO 2007/076523 A2 (CENTOCOR INC [US]; AMEGADZIE BERNARD [US]; BENSON JACQUELINE [US]; HUA) 5 July 2007 (2007-07-05) See e.g. example 1	1-17

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/018293

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		JP 2013542209 A	21-11-2013
		KR 20130130713 A	02-12-2013
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		WO 2012048134 A2	12-04-2012
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		AU 2010315557 A1	20-09-2012
		CA 2778112 A1	12-05-2011
		CN 102741285 A	17-10-2012
		CO 6531481 A2	28-09-2012
		EA 201270571 A1	28-09-2012
		EP 2493925 A1	05-09-2012
		JP 2013507991 A	07-03-2013
		KR 20120090091 A	16-08-2012
		MA 33757 B1	01-11-2012
		PE 15792012 A1	13-12-2012
		TW 201121567 A	01-07-2011
		US 2013004501 A1	03-01-2013
		UY 32971 A	30-11-2010
		WO 2011056600 A1	12-05-2011
WO 2008103473 A1	28-08-2008	CA 2678863 A1	28-08-2008
		CN 101663320 A	03-03-2010
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		SG 178804 A1	29-03-2012
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WO 2012045848 A1	12-04-2012	AU 2011311482 A1	04-04-2013
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		EP 2625199 A1	14-08-2013
		JP 2013543501 A	05-12-2013
		KR 20130110179 A	08-10-2013
		MA 34646 B1	02-11-2013

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/018293

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		TW 201216984 A	01-05-2012
		US 2013202610 A1	08-08-2013
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		US 2009270480 A1	29-10-2009
		WO 2007076523 A2	05-07-2007

(19)中华人民共和国国家知识产权局

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(43)申请公布日 2015.12.30

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(22)申请日 2014.02.25
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2015.09.15
(86)PCT国际申请的申请数据
PCT/US2014/018293 2014.02.25
(87)PCT国际申请的公布数据
WO2014/149425 EN 2014.09.25
(71)申请人 美国安进公司
地址 美国加利福尼亚州
(72)发明人 J.P.吉布斯 W.楚吉 W-J.潘
(74)专利代理机构 中国专利代理(香港)有限公司 72001
代理人 黄登高 彭昶
(51)Int.Cl.
A61K 39/00(2006.01)
A61K 39/395(2006.01)
C07K 16/24(2006.01)

权利要求书2页 说明书16页
序列表2页 附图7页

(54)发明名称

使用抗IL-23抗体治疗银屑病的方法

(57)摘要

本发明涉及用于治疗银屑病的产品和方法。所述产品涉及抑制天然人IL-23同时保留IL-12的抗体。一个实施例描述了用以在健康受试者和患有中度到重度银屑病的受试者中评价抗IL-23抗体(AMG139)的安全性、耐受性、药物动力学及药效学的1期、随机化、双盲、安慰剂对照的递增单次剂量研究。

V_H1 (SEQ ID NO: 1)

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNEYYADSVKGR
CDR 1 CDR 2

FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGYTSSWYPDAFDIWGQGTMVTVSS
CDR 3

V_L1 (SEQ ID NO: 2)

QSVLTQPPSVSGAPGQRVTISCTGSSSNTGAGYDVHWYQQVPGTAPKLLIYGSGNRPS
CDR 1 CDR 2

GVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSGWVFGGGTRLTVL
CDR 3

CN 105209064 A

1.一种治疗有需要的受试者的银屑病的方法,所述方法包括向所述受试者施用抗IL-23抗体,其量和时间间隔是:

a. 每0.5-1.5个月15-54mg;

b. 每1.5-4.5个月55-149mg;

c. 每4-8个月150-299mg;或

d. 每4-12个月300-1100mg。

2.如权利要求1所述的方法,其中所述量和时间间隔是:

a. 每0.5-1.0个月15-21mg;

b. 每1.5-3.0个月55-70mg;

c. 每4-6个月150-260mg;或

d. 每4-8个月300-700mg。

3.如权利要求1所述的方法,其中所述量和时间间隔是:

a. 每个月21mg;

b. 每3个月70mg;

c. 每6个月210mg;或

d. 每6个月700mg。

4.如权利要求1所述的方法,其中所述量和时间间隔是:

a. 每3个月210mg;或

b. 每3个月700mg。

5.如权利要求1所述的方法,其中所述量和时间间隔是:

a. 每1个月210mg;或

b. 每1个月700mg。

6.一种治疗有需要的受试者的银屑病的方法,所述方法包括向所述受试者施用一定量的抗IL-23抗体,其量和时间间隔足以实现和/或维持每体积血清介于12.5ng/ml与1000ng/ml之间的抗IL-23抗体量。

7.如权利要求6所述的方法,其中所述每体积血清的抗IL-23抗体量是至少10ng/ml。

8.如权利要求6所述的方法,其中所述每体积血清的抗IL-23抗体量是选自由以下各量组成的群组:至少25ng/ml;至少50ng/ml;至少60ng/ml;至少70ng/ml;至少75ng/ml;及至少80ng/ml。

9.如权利要求6所述的方法,其中所述每体积血清的抗IL-23抗体量介于85ng/ml与100ng/ml之间。

10.如权利要求6所述的方法,其中所述每体积血清的抗IL-23抗体量介于70ng/ml与150ng/ml之间。

11.如权利要求6所述的方法,其中所述每体积血清的抗IL-23抗体量介于50ng/ml与250ng/ml之间。

12.如权利要求6所述的方法,其中所述每体积血清的抗IL-23抗体量介于40ng/ml与500ng/ml之间。

13.如权利要求6所述的方法,其中所述每体积血清的抗IL-23抗体量介于25ng/ml与750ng/ml之间。

14. 如权利要求 6 所述的方法，其中所述每体积血清的抗 IL-23 抗体量介于 10ng/ml 与 1,000ng/ml 之间。

15. 如以上权利要求中任一项所述的方法，其中所述抗 IL-23 抗体是 IV 施用的。

16. 如以上权利要求中任一项所述的方法，其中所述抗 IL-23 抗体是 SC 施用的。

17. 如以上权利要求中任一项所述的方法，其中所述抗 IL-23 抗体是 AMG 139。

使用抗 IL-23 抗体治疗银屑病的方法

发明领域

[0001] 本发明涉及用于治疗银屑病的产品和方法。所述产品涉及抑制天然人 IL-23 同时保留 IL-12 的抗体。

[0002] 背景

[0003] 银屑病是一种常见的慢性特发性皮肤发炎性疾病。它影响了 1％到 2％的白种人，包括～ 2500 万的北美人和欧洲人。遗传和环境因素在银屑病的发病机理中起到关键作用，其组织病理学特征在于 :表皮明显变厚、角化细胞增殖和分化改变以及类似于在创伤修复中所观察到的遗传程序。角化细胞反应的这一变化被认为是由细胞免疫系统活化所引起，并且多项研究已在疾病的发病机理中涉及到 T 细胞、树突状细胞以及各种炎性细胞因子和趋化因子 (Nestle FO,Kaplan DH 等人,Psoriasis,N Engl J Med.2009 ;361(5):496-509 ; Griffiths CE 和 Barker JN.Lancet.2007 ;370(9583):263-271 ;Lowes MA，BowcockAM 等人,Nature.2007 ;445(7130):866-873 ;Nickoloff BJ 和 Nestle FO.J Clin Invest.2004 ; 113(12):1664-1675。

[0004] 在银屑病的病变组织中，白细胞介素 23(IL-23) 的表达增加。IL-23 是一种异源二聚体细胞因子，而且还是促炎性细胞因子的有效诱导剂。IL-23 与异源二聚体细胞因子白细胞介素 12(IL-12) 相关，二者共有共同的 p40 亚基。在 IL-23 中，独特的 p19 亚基与 p40 亚基共价结合。在 IL-12 中，独特亚基是 p35(Oppmann 等人，Immunity，2000,13:713-715)。同样，IL-23 是由抗原呈递细胞（如树突状细胞和巨噬细胞）响应如 CD40 连接、Toll 样受体激动剂及病原体等活化刺激物来表达。IL-23 结合于包含 IL-12Rβ1 亚基（与 IL-12 受体共有）和独特受体亚基 IL-23R 的异源二聚体受体。

[0005] IL-23 作用于活化的记忆性 T 细胞并促进 T 细胞亚群 Th17 的存活和扩增。Th17 细胞产生促炎性细胞因子，包括 IL-6、IL-17、TNFα、IL-22 及 GM-CSF。IL-23 还作用于自然杀伤细胞、树突状细胞和巨噬细胞以诱导促炎性细胞因子的表达。与 IL-23 不同，IL-12 诱导原生 CD4+T 细胞分化成产生 Th1 IFNγ 的成熟效应细胞，并且通过刺激 IFNγ 产生来诱导 NK 和细胞毒性 T 细胞功能。先前认为由 IL-12 驱动的 Th1 细胞对于许多自体免疫疾病来说是致病性 T 细胞亚群，然而，在近期关于发炎性肠病、银屑病、发炎性关节炎及多发性硬化症的动物模型研究中评价了 IL-12 与 IL-23 各自的贡献，并且已经坚定地确定，IL-23 而非 IL-12 是自体免疫疾病 / 发炎性疾病的重要致病因素 (Ahern 等人，Immun. Rev.2008 226:147-159 ;Cua 等人，Nature 2003 421:744-748 ;Yago 等人，Arthritis Res and Ther.2007 9(5):R96)。相信 IL-12 在针对许多细胞内病原体和病毒的保护性先天免疫反应和适应性免疫反应的产生方面以及在肿瘤免疫监测方面起到关键作用。参见 Kastelein 等人,Annual Review ofImmunology,2007,25:221-42 ;Liu 等人,Rheumatology, 2007,46(8):1266-73 ;Bowman 等 人，Current Opinion in Infectious Diseases,2006 19:245-52 ;Fieschi 和 Casanova，Eur.J.Immunol.2003 33:1461-4 ;Meeran 等 人，Mol. Cancer Ther.2006 5:825-32 ;Langowski 等人，Nature 2006 442:461-5。因此，相较于 IL-12 和 IL-23 的双重抑制作用，IL-23 特异性抑制作用（保留 IL-12 或共有的 p40 亚基）

应当具有可能更优良的安全性特征。

[0006] 如与非病变皮肤相比较，在银屑病的病变皮肤中 IL-23p19 和 IL-12/23p40 mRNA 增加；分别平均增加 22 倍和 12 倍。IL-12p35mRNA 的表达在成对病变皮肤与非病变皮肤之间无显著不同 (Lee E,Trepicchio WL 等人，J Exp Med.2004；199(1):125-130)。这些数据表明，IL-23 在银屑病的病变组织中上调，而 IL-12 则不然。也已经通过免疫组织化学分析证实，IL-23 蛋白质在银屑病的病变皮肤中上调。抗 IL-23p19 抗体染色显示，相较于正常皮肤（和非病变皮肤），在银屑病病变皮肤的表皮和真皮中表达都增加 (Piskin G，Sylva-Steenland RM 等人，In vitro and in situ expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions:enhanced expression in psoriatic skin.J Immunol.2006；176(3):1908-1915)。IL-23 的水平随有效疾病治疗 (UV 治疗或抗 TNF 治疗）后引起的 PsO 临床改善而降低，从而证明 IL-23 的过量产生与活动性银屑病之间具有直接相关性 (Fitch E，Harper E 等人，Pathophysiology of psoriasis:recent advances on IL-23 and Th17 cytokines.Curr Rheumatol Rep.2007；9(6):461-4)。

[0007] 在银屑病患者中，使用总计 >25,000 个主要功能性 SNP 以 3 个独立的病例对照样品集进行全基因关联研究。在这一研究中，发现与 IL-12/23p40 的 3’UTR 中的 SNP 存在特别显著的关联性。对 IL-12(p35) 和 IL-23(p19) 配体和受体链 (IL-12Rβ1、IL-12Rβ2 和 IL-23R) 中的多个 SNP 分别进行基因分型。IL-23R 中的两个 SNP 与银屑病高度关联，而与其它配体和受体链无关联 (Cargill M，Schrodi SJ 等人，Am J Hum Genet.2007；80(2):273-290)。有关 IL-12/23p40 和 IL-23R 中的常见变体与银屑病风险相关的发现提供了遗传学证据，证实 IL-23 路径在银屑病发病机理中起到重要作用。

[0008] 当前批准用于银屑病的疗法包括外敷药剂（例如，皮质类固醇类、煤焦油制剂类、类视色素类、光照疗法）；全身疗法（例如甲氨蝶呤 (methotrexate)、类视色素类、环孢菌素 (cyclosporin)）；及生物制剂（例如依他普特 (etanercept)、阿达木单抗 (adalimumab)、阿法赛特 (alefacept)、优特克单抗 (ustekinumab)）。尽管有这些可用的疗法，但许多患者仍未得到治疗，对疗法不起反应，或经历与全身疗法或光照疗法相关的毒性，并出现显著皮肤问题和残疾。

[0009] 本文中预期，需要特异性靶向 IL-23，而无与 IL-12 抑制相关的潜在风险的新颖银屑病治疗模式。本文提供了使用能够抑制天然人 IL-23 而保留 IL-12 的完全人类治疗剂来治疗银屑病的方法。

[0010] 发明概述

[0011] 本文提供了一种治疗有需要的受试者的银屑病的方法，所述方法包括向所述受试者施用抗 IL-23 抗体，其量和时间间隔是：每 0.5－1.5 个月 15－54mg；每 1.5－4.5 个月 55－149mg；每 4－8 个月 150－299mg；或每 4－12 个月 300－1100mg。在一些实施方案中，所述量和时间间隔是：每 0.5－1.0 个月 15－21mg；每 1.5－3.0 个月 55－70mg；每 4－6 个月 150－260mg；或每 4－8 个月 300－700mg。在一些实施方案中，所述量和时间间隔是：每个月 21mg；每 3 个月 70mg；每 6 个月 210mg；或每 6 个月 700mg。在一些实施方案中，所述量和时间间隔是：每 3 个月 210mg 或每 3 个月 700mg。在一些实施方案中，所述量和时间间隔是：每 1 个月 210mg 或每 1 个月 700mg。在所述方法的一些实施方案中，抗 IL23 抗体是

IV 施用的。在所述方法的一些实施方案中，抗 IL23 抗体是 SC 施用的。在所述方法的一些实施方案中，抗 IL-23 抗体是 AMG 139。

[0012] 本文还提供了一种治疗有需要的受试者的银屑病的方法，所述方法包括向所述受试者施用一定量的抗 IL-23 抗体，其量和时间间隔足以实现和 / 或维持每体积血清介于 12.5ng/ml 与 1000ng/ml 之间的抗 IL-23 抗体量。在一些实施方案中，每体积血清的抗 IL-23 抗体量是至少 10ng/ml。在一些实施方案中，每体积血清的抗 IL-23 抗体量是选自由以下各量组成的群组 ：至少 25ng/ml ；至少 50ng/ml ；至少 60ng/ml ；至少 70ng/ml ；至少 75ng/ml ；及至少 80ng/ml。在一些实施方案中，每体积血清的抗 IL-23 抗体量介于 85ng/ml 与 100ng/ml 之间。在一些实施方案中，每体积血清的抗 IL-23 抗体量介于 70ng/ml 与 150ng/ml 之间。在一些实施方案中，每体积血清的抗 IL-23 抗体量介于 50ng/ml 与 250ng/ml 之间。在一些实施方案中，每体积血清的抗 IL-23 抗体量介于 40ng/ml 与 500ng/ml 之间。在一些实施方案中，每体积血清的抗 IL-23 抗体量介于 25ng/ml 与 750ng/ml 之间。在一些实施方案中，每体积血清的抗 IL-23 抗体量介于 10ng/ml 与 1,000ng/ml 之间。在所述方法的一些实施方案中，抗 IL23 抗体是 IV 施用的。在所述方法的一些实施方案中，抗 IL23 抗体是 SC 施用的。在所述方法的一些实施方案中，抗 IL-23 抗体是 AMG 139。

[0013] 附图简要说明

[0014] 图 1 呈现了有关在健康受试者 (healthy subject，HS) 中皮下施用 AMG 139 所进行的递增单次剂量研究的药物动力学分析的结果。所示结果说明了平均 (±SD) 血清 AMG 139 浓度 - 时间曲线。

[0015] 图 2 呈现了有关在健康受试者 (HS) 中静脉内施用 AMG 139 所进行的递增单次剂量研究的药物动力学分析的结果。所示结果说明了平均 (±SD) 血清 AMG 139 浓度 - 时间曲线。

[0016] 图 3 呈现了有关在银屑病受试者 (PsO) 中皮下施用 AMG 139 所进行的递增单次剂量研究的药物动力学分析的结果。所示结果说明了平均 (±SD) 血清 AMG 139 浓度 - 时间曲线。

[0017] 图 4 呈现了有关在银屑病受试者 (PsO) 中静脉内施用 AMG 139 所进行的递增单次剂量研究的药物动力学分析的结果。所示结果说明了平均 (±SD) 血清 AMG 139 浓度 - 时间曲线。

[0018] 图 5 呈现了有关单次递增剂量研究中的 PsO 受试者的银屑病皮损面积和严重程度指数 (Psoriasis Area and Severity Index，PASI) 评分评估的结果。所示结果说明了在整个研究中各时间点时的平均 PASI 评分 (±SD)。

[0019] 图 6 呈现了有关单次递增剂量研究中的 PsO 受试者的银屑病皮损面积和严重程度指数 (PASI) 评分评估的结果 (针对基线标准化)。所示结果说明了在整个研究中各时间点时相对于基线的平均 PASI 评分改善 (±SD)。

[0020] 图 7 呈现了基于实施例 1 的数据开发 AMG 139 定量种群 PK 模型时所使用的药物动力学结构模型。

[0021] 图 8 呈现了有关 AMG 139 种群 PK 模型的诊断性可视化预测检查的结果。所示结果说明了在模拟 1000 次临床试验之后的平均值 (实线) 和 90％置信区间 (虚线)AMG 139 浓度 - 时间曲线。每个点表示受试者的实际观测浓度。

[0022] 图 9 呈现了有关 AMG 139 种群 PK 模型的多次诊断性可视化预测检查的结果。结果说明了 AMG 139 的观测浓度与种群和个体预测浓度之间的相关性，以及种群预测浓度与时间之间模型拟合的加权残量。

[0023] 图 10 呈现了体重与 PK 参数之间的相关性分析的结果。结果说明了对于健康受试者和 PsO 受试者的组合群体，个体的 CL 和 V 与体重呈正相关。

[0024] 图 11 呈现了 AMG 139 重链可变区和轻链可变区的氨基酸序列。

[0025] 发明详述

[0026] 本文提供了用于治疗有需要的受试者的银屑病的方法，所述方法包括向所述受试者施用一定量的特异性结合 IL-23 的人单克隆抗体。在一些实施方案中，抗 IL-23 抗体特异性结合 IL-23，但保留 IL-12。

[0027] 本文中使用的术语“治疗 (treating/treatment)”一般是指获得所希望的药理学、生理学或治疗作用。该作用就预防或部分预防疾病、其症状或病况来说可以是预防性的，和 / 或就部分或完全治愈疾病、病况、症状或由该疾病引起的副作用来说可以是治疗性的。如本文中所使用，术语“治疗”涵盖哺乳动物，特别是人类疾病的任何治疗，并且包括 :(a) 防止可能易患该疾病但尚未诊断出患有该疾病的受试者发生该疾病 ;(b) 抑制该疾病，即，使其发展停滞 ;或 (c) 减轻该疾病，即，使该疾病和 / 或其症状或病况消退。本发明是针对治疗罹患病理炎症相关性疾病的患者。本发明涉及在较长时间段内预防、抑制或减轻由病理炎症引起的副作用，和 / 或在较长时间段内预防、抑制或减轻由对生物系统中存在的不当炎症的生理反应所引起的副作用。

[0028] 在一个方面，本发明提供了治疗受试者的方法。该方法可以例如对受试者具有大体上有益健康的作用，例如，该方法可以增加受试者的预期寿命。或者，该方法可以例如治疗、预防、治愈、减轻或缓解 (“治疗”) 疾病、病症、病况或不适 (“病况”)。在一个实施方案中，本发明提供了一种治疗受试者的病况的方法，该方法包括向该受试者施用包含特定抗体的药物组合物，其中该病况可以通过降低受试者体内 IL-23 的活性 (部分或完全降低) 进行治疗。治疗涵盖治疗性用药 (即，当疾病或病况的病征和症状明显时用药) 和预防性或维持性疗法 (即，当疾病或病况被遏制时用药)，以及进行治疗以诱导症状缓解和 / 或维持症状缓解。因此，疾病或病况的严重程度可以减轻 (部分、显著或完全减轻)，或者病征和症状可以得到预防或延缓 (延缓发作、延长症状缓解，或被遏制)。

[0029] 在打算根据本发明治疗的病况中有与 IL-23 相关或 IL-23 在引起潜在疾病或病症或者以其它方式引起不良症状方面起作用的病况。这些病况包括皮肤病症，如银屑病、斑块状银屑病、点滴状银屑病、皮褶银屑病、脓疱性银屑病、红皮病型银屑病、皮炎及特异性皮炎。

[0030] 如本文所使用，术语“功效”在剂量方案情形中是指特定治疗方案的有效性。功效可以基于疾病过程对本发明的药剂起反应而发生的改变进行测量。在一个实施方案中，将抗原结合蛋白 (例如，抗 IL-23 抗体) 以一定量并且经一段时间施用给受试者，所述量和时间足以诱导至少一种反映所治疗病症的严重程度的指标的改善，优选是持续改善。可以对反映受试者不适、疾病或病况的各种指标进行评估以确定治疗量和时间是否足够。这些指标包括例如临床上认可的有关疾病严重程度、症状或所论及的病症的表现的指标。

[0031] 在一个实施方案中，如果受试者在间隔两到四周的至少两个时间内展现改善，则

该改善被认为是持续的。在另一个实施方案中，如果受试者在间隔两到四个月的至少两个时间内展现改善，则该改善被认为是持续的；在又一实施方案中，如果受试者在间隔六到十二个月的至少两个时间内展现改善，则该改善被认为是持续的。改善的程度一般是由医师基于病征、症状、活检或其它测试结果决定，并且医师还可以采用递交给受试者的调查表进行，如针对给定疾病所开发的生活质量调查表。

[0032] 可施用 IL-23 特异性抗体以实现受试者病况的改善。改善可以通过疾病活动性指数的降低、通过临床症状的缓解或通过有关疾病活动性的其它量度来指示。一种此类疾病指数是银屑病皮损面积和严重程度指数 (PASI)。PASI 是对病变的平均发红程度、厚度和起鳞程度的一种度量，分别基于 0-4 分量表分级，并以受累的面积进行加权。银屑病靶病变评估评分 (Psoriasis Target LesionAssessment Score) 是用于评估个体皮肤病变的严重程度的指数。该评分是基于针对斑块隆起、鳞屑量和范围或红斑范围，以及靶病变对治疗的反应的评价总和。另一疾病指数是美国银屑病基金会银屑病评分 (National Psoriasis Foundation Psoriasis Score，NSF-PS)。改善的程度一般是由医师基于病征、症状 (如医师整体评估 (PGA))、总体病变评估 (OLA)、活检、全身照片或其它测试结果决定，并且医师还可以采用递交给受试者的调查表进行，如针对给定疾病所开发的生活质量调查表。

[0033] 在一个实施方案中，如果受试者在间隔两到四周的至少两个时间内展现改善，则该改善被认为是持续的。在另一个实施方案中，如果受试者在间隔两到四个月的至少两个时间内展现改善，则该改善被认为是持续的；在又一实施方案中，如果受试者在间隔六到十二个月的至少两个时间内展现改善，则该改善被认为是持续的。在另一个实施方案中，当受试者的 PASI 评分展现至少 50％、55％、60％、65％、70％、75％、80％、85％、90％、95％或 100％改善时，认为实现改善。

[0034] 用 IL-23 特异性抗体治疗受试者可以按一定量和 / 或充足时间间隔进行，以实现和 / 或维持每体积血清一定量的 IL-23 特异性抗体，例如，使用本文所描述的检验测定。举例来说，给予的异源二聚体特异性抗体达到 12.5ng/ml 到 1000ng/ml。在一个实施方案中，给予的异源二聚体特异性抗体达到至少 12.5ng/ml、25ng/ml、50ng/ml、60ng/ml、70ng/ml、75ng/ml、80ng/ml、85ng/ml、90ng/ml、95ng/ml、100ng/ml、150ng/ml、200ng/ml、500ng/ml 或 990ng/ml。本领域技术人员应了解，此处所给的量适用于全长抗体或免疫球蛋白分子；如果使用其抗原结合片段，则绝对量将不同于所给量，其量可以基于片段的分子量计算。

[0035] 用 IL-23 特异性抗体治疗受试者可以按以下量和时间间隔进行：每 0.5 - 1.5 个月 15 - 54mg；每 1.5 - 4.5 个月 55 - 149mg；每 4-8 个月 150 - 299mg；或每 14-8 个月 300 - 1100mg。在一个实施方案中，所述量和时间间隔选自由以下各量组成的群组：每个月 21mg；每 3 个月 70mg；每 6 个月 210mg；或每 6 个月 700mg。

[0036] 如通过 PASI 评分系统所测量，皮下和静脉内施用 AMG139 使银屑病的症状显著减轻。在一些实施方案中，使用以上所描述的 AMG139 施用剂量和施用时程可以使银屑病患者的 PASI 评分降低至少 10％、15％、20％、25％、30％、35％、40％、45％、50％、55％、60％、65％、70％、75％、80％、85％、90％、95％或 100％。

[0037] 应了解，本文所描述的疾病治疗方法将施用有效量的抗 IL-23 抗体。取决于待治疗的适应症，治疗有效量应足以使所靶向的病理病况的至少一种症状相对于未治疗的受试者减轻至少约 5％、10％、15％、20％、25％、30％、35％、40％、45％、50％、55％、60％、65％、

70％、75％、80％、85％、90％、95％或更高百分比。

[0038] 可以调整抗 IL-23 抗体的施用和剂量方案以提供有效得到最佳治疗反应的量。举例来说，可以施用单次推注；可以随时间施用若干分次剂量；或可以如治疗情况的紧急性所指示，按比例减小或增加剂量。抗 IL-23 抗体可以通过任何适合技术施用，包括但不限于，通过肠胃外、外敷或吸入施用。如果是注射，则药物组合物可以例如经由关节内、静脉内、肌肉内、病变内、腹膜内或皮肤途径（包括真皮内、透皮或真皮下，及皮下）、推注或连续输注施用。在一些实施方案中，药物组合物是通过静脉内途径施用。在一些实施方案中，药物组合物是通过皮下途径施用。在其它实施方案中，这些组合物是通过口服、口颊、直肠、气管内、胃或颅内途径施用。对于涉及胃肠道的病况，涵盖例如通过灌肠剂或栓剂在例如疾病或损伤部位局部施用。还涵盖透皮递送和由植入剂持续释放。通过吸入递送包括例如经鼻或经口吸入、使用雾化剂、吸入呈气雾剂形式的拮抗剂等等。其它替代方案包括滴眼液；口服制剂，包括丸剂、糖浆、锭剂或咀嚼胶；以及外敷制剂，如洗液、凝胶、喷雾剂及油膏。

[0039] IL-23 抗体宜以包含一种或多种另外的组分（如生理学上可接受的载剂、赋形剂或稀释剂）的组合物形式施用。任选地，该组合物另外包含一种或多种生理活性剂用于组合疗法。药物组合物可以包含抗 IL-23 抗体以及一种或多种物质，这些物质选自由以下各物组成的群组：缓冲剂；抗氧化剂，如抗坏血酸；低分子量多肽（如具有少于 10 个氨基酸的多肽）；蛋白质；氨基酸；碳水化合物，如葡萄糖、蔗糖或糊精；螯合剂，如 EDTA；谷胱甘肽；稳定剂；及赋形剂。中性缓冲生理盐水或混有同种血清白蛋白的生理盐水是适当稀释剂的实例。根据适当行业标准，还可以添加防腐剂，如苯甲醇。该组合物可以使用适当赋形剂溶液（例如蔗糖）作为稀释剂配制成冻干产物形式。提供的抗 IL-23 抗体的浓度可以是 50mg/ml 到 200mg/ml。可用于本发明中的示例性制剂是包括适当 pH 值 (4.5 到 5.2) 的谷氨酸、柠檬酸或乙酸缓冲液；适当浓度（如 1％到 20％ (w/v)）赋形剂，如蔗糖、甘氨酸、脯氨酸、甘油和 / 或山梨糖醇；以及 0.001％ -0.1％ (w/v) 的适当浓度表面活性剂，如非离子型表面活性剂，如聚山梨醇酯（聚山梨醇酯 20 或 80）或泊洛沙姆 (poloxamer)（泊洛沙姆 1888）的制剂。这些制剂公开于美国专利号 6171586 以及 WIPO 公开的申请号 WO20100027766 和 WO2011088120 中。在一些实施方案中，制剂包含乙酸钠、蔗糖和聚山梨醇酯 20。在一些实施方案中，制剂包含 70mg/mLAMG 139、10mM 乙酸钠、9％ (w/v) 蔗糖及 0.004％ (w/v) 聚山梨醇酯 20，pH 5.2。适合的组分在所采用的剂量和浓度下对接受者无毒。可以用于药物制剂中的组分的其它实例见于包括第 21 版 (2005) 在内的任何《雷氏药学大全》(Remington's Pharmaceutical Sciences)(Mack Publishing Company, Easton, PA) 中。

[0040] 医务人员使用的试剂盒包括抗 IL-23 抗体以及有关用于治疗本文所论述的任何病况的标记或其它说明。在一个实施方案中，试剂盒包括一种或多种 IL-23 结合抗原结合蛋白的无菌制剂，该制剂可以呈如以上所论述的组合物的形式，并且可以装在一个或多个小瓶中。

[0041] 本发明方法的特定实施方案涉及使用抗 IL-23 抗体以及一种或多种另外的 IL-23 拮抗剂，如美国专利 US 7,491,391、US 7,807,414、US7,872,102、US7,807,160、US8362212、US7,935,344、US 7,790,862、US2012282269；美国公开的专利申请 US 2009-0123479、US 20120128689 及 US2012264917；以及 WIPO 公开 WO1999/05280、WO 2007/0244846、WO2007/027714、WO 2007/076524、WO2007/147019、WO2008/103473、WO 2008/103432、

WO2009/043933、WO2009/082624、WO 12/009760 中所描述。

[0042] 还提供了单独施用或与可用于治疗患者所患病况的其它药剂组合施用的 IL-23 抗体。外敷药物（例如，类固醇类、煤焦油、蒽三酚、死海浴盐、各种天然油、维生素 D3 及其类似物、阳光、外敷用类视色素）、光照疗法（例如，紫外光、光化学疗法 (PUVA)）及内服药物（例如，甲氨蝶呤、全身性类固醇、口服类视色素、环孢菌素）。当共施用多种治疗剂时，如相关领域中所了解或已知的，可以相应地调整剂量。

[0043] 在使用分子和 / 或其它治疗的组合的任何情况下，个别分子和 / 或治疗可以按任何次序，经任何时间长度施用，使其例如同时、连续地或交替地起效。在一个实施方案中，治疗方法包括完成第一疗程用一个分子或其它治疗进行的治疗，随后开始第二个疗程。第一个疗程结束与第二个疗程开始之间的时间长度可以是使总疗程有效的任何时间长度，例如数秒、数分钟、数小时、数天、数周、数月或甚至数年。

[0044] 术语“多肽”或“蛋白质”意思指具有天然蛋白质（即，由天然存在并且非重组的细胞产生的蛋白质）的氨基酸序列的大分子；或其是由遗传工程改造的细胞或重组细胞产生，并且包含具有天然蛋白质的氨基酸序列的分子，或在天然序列中具有一个或多个氨基酸残基缺失、插入和 / 或取代的分子。该术语还包括一个或多个氨基酸是相应天然存在的氨基酸和聚合物的化学类似物的氨基酸聚合物。术语“多肽”和“蛋白质”涵盖 IL-23 抗体以及在抗原结合蛋白序列中具有一个或多个氨基酸残基缺失、添加和 / 或取代的序列。术语“多肽片段”是指相较于全长天然蛋白质，具有氨基酸末端缺失、羧基末端缺失和 / 或内部缺失的多肽。此类片段还可以含有相较于天然蛋白质存在修饰的氨基酸。在某些实施方案中，片段的长度是约 5 到 500 个氨基酸。举例来说，片段的长度可以是至少 5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、50、70、100、110、150、200、250、300、350、400 或 450 个氨基酸。有用的多肽片段包括抗体的免疫功能性片段，包括结合结构域。就抗 IL-23 抗体来说，有用的片段包括但不限于，一个或多个 CDR 区、重链或轻链的可变结构域、抗体链的一部分、包括不到三个 CDR 的可变区的一部分等。

[0045] 术语“分离的蛋白质”是指从蛋白质或多肽，或者会干扰治疗、诊断、预防、研究或其它用途的其它污染物纯化的蛋白质，如抗原结合蛋白（其实例可以是抗体）。如本文中所使用，“基本上纯”意思指，所描述的分子物质是所存在的占主导的物质，也就是说，以摩尔量计，其比同一混合物中的任何其它个别物质含量高。在某些实施方案中，基本上纯的分子是目标物质占存在的所有大分子物质至少 50％（以摩尔量计）的一种组合物。在其它实施方案中，基本上纯的组合物将占该组合物中存在的所有大分子物质至少 80％、85％、90％、95％或 99％。在某些实施方案中，基本上均质的物质已经纯化达到无法通过常规检测方法检测到组合物中的污染性物质并因此该组合物由单一可检测的大分子物质组成的程度。

[0046] 多肽（例如抗原结合蛋白，如抗体）的“变体”包含这样的氨基酸序列，其中相对于另一多肽序列，该氨基酸序列中插入、缺失和 / 或取代入一个或多个氨基酸残基。变体包括融合蛋白。多肽的“衍生物”是通过与插入、缺失或取代变体不同的某种方式，例如经由与另一化学部分偶联来进行化学修饰的多肽。

[0047] 如本说明书通篇结合如多肽、核酸、宿主细胞等生物材料使用的术语“天然存在的”或“天然的”是指在自然界中发现的材料，如天然人 IL-23。在某些方面，提供了结合天然 IL-23 的重组抗原结合蛋白。在这种情况下，“重组蛋白”是使用重组技术，即，通过表达

本文所描述的重组核酸制备的一种蛋白质。用于制备重组蛋白的方法和技术是本领域中众所周知的。

[0048] 术语“抗体”是指任何同种型的完整免疫球蛋白，或其可以与完整抗体竞争特异性结合到靶抗原的片段，并且包括例如嵌合抗体、人源化抗体、完全人类抗体及双特异性抗体。因此，抗体是一种抗原结合蛋白。除非另作指示，否则术语“抗体”除包含两个全长重链和两个全长轻链的抗体外，还包括其衍生物、变体、片段及突变蛋白，其实例于下文描述。完整抗体一般将包含至少两个全长重链和两个全长轻链，但在一些情况下，可以包括较少链，如骆驼科中天然存在的抗体，这些抗体可以仅包含重链。抗体可以仅源自于单一来源，或者可以是“嵌合的”，即，抗体的不同部分可以源自于两种不同的抗体，以下将进一步描述。抗原结合蛋白、抗体或结合片段可以在杂交瘤中产生，通过重组 DNA 技术产生，或通过酶促裂解或化学裂解完整抗体产生。

[0049] 如本文所使用，术语抗体或免疫球蛋白链（重链或轻链）的“功能片段”（或简称为“片段”）是包含中缺乏全长链中存在的至少一些氨基酸的抗体的一部分（不管这一部分是如何获得或合成的）但能够特异性结合到抗原的一种抗原结合蛋白。此类片段具有生物活性，因为这些片段特异性结合到靶抗原并且可以与其它抗原结合蛋白（包括完整抗体）竞争特异性结合到给定表位。在一个方面，此类片段将保留至少一个存在于全长轻链或重链中的 CDR，并且在一些实施方案中将包含单一重链和 / 或轻链或其部分。这些生物活性片段可以通过重组 DNA 技术产生，或者可以通过酶促裂解或化学裂解抗原结合蛋白（包括完整抗体）产生。片段包括但不限于，免疫功能性片段，如 Fab、Fab’、F(ab’)2、Fv、结构域抗体及单链抗体，并且可以源自于任何哺乳动物来源，包括但不限于，人类、小鼠、大鼠、骆驼或兔。另外预期本文所公开的抗原结合蛋白的功能性部分，例如一个或多个 CDR，可以与另一种蛋白质或与小分子共价结合以产生针对体内特定靶的治疗剂，具有双功能治疗特性，或具有较长的血清半衰期。

[0050] 如本文所使用，“抗原结合蛋白”意思指特异性结合指定靶抗原的蛋白质；本文所提供的抗原是 IL-23，特别是人 IL-23，包括天然人 IL-23。本文所提供的抗原结合蛋白与 IL-23 的独特 p19 亚基的至少一部分相互作用，可检测地结合 IL-23；但与 IL-12（例如 IL-12 的 p40 和 / 或 p35 亚基）的结合不具有任何显著性，因此“保留 IL-12”。因此，本文提供的抗原结合蛋白能够影响 IL-23 活性，而没有可能引起 IL-12 或共有 p40 亚基抑制的潜在风险。抗原结合蛋白可以例如通过影响与受体的结合，如通过干扰受体缔合，来影响 IL-23 与其受体相互作用的能力。明确地说，此类抗原结合蛋白完全地或部分地降低、抑制、干扰或调节 IL-23 的一种或多种生物活性。相较于在不存在抗原结合蛋白情况下的反应，此类抑制作用或中和作用在抗原结合蛋白存在下破坏生物反应，并且可以使用本领域中已知以及本文所描述的检验测定。本文提供的抗原结合蛋白抑制 IL-23 诱导的促炎性细胞因子产生，例如全血细胞中 IL-23 诱导的 IL-22 产生以及 NK 和全血细胞中 IL-23 诱导的 IFNγ 表达。生物活性可以降低约 20％、30％、40％、50％、60％、70％、80％、85％、90％、91％、92％、93％、94％，95％、96％、97％、98％、99％或更高百分比。

[0051] 本文所描述的某些抗原结合蛋白是抗体，或源自于抗体。此类抗原结合蛋白包括但不限于，单克隆抗体、双特异性抗体、微型抗体、结构域抗体、合成抗体、抗体模拟物、嵌合抗体、人源化抗体、人类抗体、抗体融合物、抗体偶联物、单链抗体，及其各自的片段。在一些

情况下，抗原结合蛋白是抗体的免疫片段（例如 Fab、Fab'、F(ab')2 或 scFv)。

[0052] 提供的某些抗原结合蛋白可以包含一个或多个如本文所描述的 CDR（例如 1、2、3、4、5、6 或更多个 CDR)。在一些情况下，抗原结合蛋白包含 (a) 多肽结构，以及 (b) 插入和 / 或接合多肽结构的一个或多个 CDR。多肽结构可以呈多种不同的形式。举例来说，该结构可以是或包含天然存在的抗体的框架，或者其片段或变体，或者可以实际上是完全合成的。以下进一步描述各种多肽结构的实例。

[0053] 当解离平衡常数 (KD) ≤ 10^{-8}M 时，认为本发明的抗原结合蛋白“特异性结合”其靶抗原。当 KD ≤ 5×10^{-9}M 时，抗原结合蛋白以“高亲和力”特异性结合抗原，并且当 KD ≤ 5×10^{-10}M 时，以“极高亲和力”特异性结合抗原。在一个实施方案中，抗原结合蛋白将以 KD ≤ 5×10^{-12}M 结合于人 IL-23，并且在另一实施方案中，其将以 KD ≤ 5×10^{-13}M 结合。在本发明的另一个实施方案中，抗原结合蛋白的 KD ≤ 5×10^{-12}M 并且 Koff 是约≤ 5×10^{-6}1/s。在另一个实施方案中，Koff ≤ 5×10^{-7}1/s。

[0054] 在将抗原结合蛋白用于治疗应用的实施方案中，抗原结合蛋白可以降低、抑制、干扰或调节 IL-23 的一种或多种生物活性，如诱导产生促炎性细胞因子。IL-23 具有许多不同的生物作用，这些生物作用可以在不同细胞类型中以许多不同的检验测量；这些检验和已知检验的实例参见例如美国专利申请号 US 2013-0004501，其公开内容通过引用并入本文中。示例性 IL-23 抗体公开于美国专利申请号 US 2013-0004501 中。

[0055] 除非另作说明，否则如本文所使用，“AMG 139”是指完整 AMG 139 免疫球蛋白或其与完整抗体竞争特异性结合的抗原结合部分。AMG 139 还包括氨基酸序列，特别是可变区，或其 CDR（不过，也涵盖恒定区的变化）与 AMG 139 相同或类似的抗体（或其片段）。举例来说，有用的 AMG 139 多肽的氨基酸序列与本文所公开的 AMG 139 多肽的氨基酸序列具有 85％、90％、92％、95％、98％、99％或 100％同一性。在另一个实施方案中，有用多肽与 AMG 139 的同一性介于 80％与 100％之间。

[0056] AMG139 是特异性识别天然人 IL-23 异源二聚体，但与人 IL-12 异源二聚体无任何显著结合的人类抗体。AMG139 抑制 IL-23 诱导的促炎性细胞因子产生，例如全血细胞中 IL-23 诱导的 IL-22 产生以及 NK 和全血细胞中 IL-23 诱导的 IFNγ 表达。在一些实施方案中，AMG 139 是具有包含 SEQ ID NO:1 中的 CDR1、CDR2 和 CDR3 的重链可变区以及包含 SEQ ID NO:2 中的 CDR1、CDR2 和 CDR3 的轻链可变区的一种分离的 IL-23 特异性抗原结合蛋白。在一些实施方案中，AMG 139 是重链可变区与 SEQ ID NO:1 具有至少 90％同一性并且轻链可变区与 SEQ ID NO:2 中的 CDR1、CDR2 和 CDR3 具有至少 90％同一性的一种分离的 IL-23 特异性抗原结合蛋白。参见 2011 年 5 月 11 日公开的 WO 2011/056600。

[0057] 在提供值的范围时，应了解，在该范围的上限与下限之间的每一中间值（除非上下文另作清楚规定，否则精确到下限单位的十分之一），以及在所陈述的范围中的任何其它陈述值或中间值或较小范围都涵盖于本发明中。较小范围的上限和下限可以独立地包括在该较小范围内，除非所陈述的范围中明确排除任何限值。当所陈述的范围包括一个或两个限值时，排除这些所包括的限值中的任一个或两个的范围也包括在本发明内。

[0058] 除非本文另作定义，否则结合本发明使用的科技术语应当具有本领域普通技术人员通常所了解的意义。另外，除非上下文另外需要，否则单数形式的术语应当包括复数形式并且复数形式的术语应当包括单数形式。一般来说，与本文所描述的细胞和组织培养、

分子生物学、免疫学、微生物学、遗传学以及蛋白质和核酸化学及杂交学结合使用的命名法及其技术是本领域中众所周知并且常用的那些。除非另作指示，否则本发明的方法和技术一般是根据本领域中众所周知的常规方法并且如本说明书全篇所引用和论述的各种通用和更具体的参考文献中所描述来进行。参见例如，Sambrook 等人，Molecular Cloning:A Laboratory Manual， 第 3 版，Cold Spring Harbor Laboratory Press,Cold Spring Harbor,N.Y.(2001)；和 Ausubel 等人，Current Protocols in Molecular Biology,Greene Publishing Associates(1992)；以及 Harlow 和 Lane,Antibodies:A Laboratory Manual，Cold Spring Harbor Laboratory Press,Cold Spring Harbor,N.Y.(1990)。酶促反应和纯化技术是根据制造商的说明、如本领域中通常所实现或如本文中所描述进行的。与本文所描述的分析化学、合成有机化学以及医学和药物化学结合使用的术语及其实验程序和技术是本领域中众所周知并且常用的那些。可以使用标准技术来进行化学合成、化学分析、药物制备、配制和递送以及患者的治疗。

[0059] 所标识的所有专利和其它出版物都通过引用的方式整体明确地并入本文中用于描述和公开例如这些出版物中所描述的可能结合本文所描述的信息使用的方法的目的。

[0060] 提供的以下实际实施例和预示性实施例是出于说明本发明的具体实施方案或特征的目的，而不是限制本发明的范围。

[0061] 实施例 1

[0062] 本实施例描述了用以在健康受试者 (HS) 和患有中度到重度银屑病的受试者 (PSO) 中评价抗 IL-23 抗体 (AMG 139) 的安全性、耐受性、药物动力学 (PK) 及药效学 (PD) 的 1 期、随机化、安慰剂对照的递增单次剂量研究；ClinicalTrials.gov 标识符：NCT01094093。

[0063] 将总计 73 位受试者随机分入该研究中；56 位健康成人随机分入 A 部分中并且接受单次 SC 剂量 (7mg、21mg、70mg 或 210mg) 或单次 IV 剂量 (210mg、420mg 或 700mg) 的 AMG 139，或者安慰剂，而 17 位患有中度到重度 PsO 的受试者随机分入 B 部分中并且接受单次 SC 剂量 (21mg、70mg 或 210mg) 或单次 IV 剂量 (700mg) 的 AMG 139，或者安慰剂，参看表 1。

[0064] 表 1. 每一组的剂量和施用途径

[0065]

组别	剂量（mg）	途径	受试者数量（AMG 139:安慰剂）
A 部分	健康受试者（HS）		
A1 组	7	SC	2 (1:1) 6 (5:1)
A2 组	21	SC	8 (6:2)
A3 组	70	SC	8 (6:2)
A4 组	210	SC	8 (6:2)
A5 组	210	IV	8 (6:2)
A6 组	420	IV	8 (6:2)
A7 组	700	IV	8 (6:2)
B 部分	患 PsO 的受试者		
B1 组	21	SC	4 (3:1)
B2 组	70	SC	4 (3:1)
B3 组	210	SC	4 (3:1)
B4 组	700	IV	4 (3:1)

[0066] 对于 A 部分，在到第 85 天（对于 A1 组、A2 组和 A3 组）以及到第 169 天（对于 A5 组、A6 组和 A7 组）的指定时间点取得连续血液样品。对于 B 部分，指定时间点对于 B1 组和 B2 组是到第 113 天（分别是 21mg 和 70mg AMG139 SC)。对于 B3 组和 B4 组是到第 169 天（分别是 210 SC 和 700IV AMG139)。

[0067] 为了测量受试者血清中 AMG 139 的量，将捕捉抗体（小鼠抗 AMG 139 1F2 mAb) 被动吸附到Multi-Array® 96 孔 HighBind 微量板各孔 (Meso Scale Discovery) 中。在去除过量的捕捉抗体之后，用 Blocker™ BLOTTO 缓冲液阻断微量板的孔。通过在 Blocker™ BLOTTO 缓冲液中稀释 100 倍来进行预处理，随后将通过外加已知量的 AMG 139 到 100％正常人血清池中所制备的标准品和质量对照样品装载到微量板的孔中，同时待测试样品和基质空白作相同处理。利用固定的捕捉抗体捕捉样品中的任何 AMG 139。通过洗涤微量板的孔来去除未结合的材料。洗涤后，将偶联 SULFO-TAGTM 的检测抗体（抗 AMG 139 1A4.1mAb) 添加到微量板的孔中以结合捕捉的 AMG 139。通过洗涤微量板的孔来去除未结合的 SULFO-TAGTM 偶联捕捉抗体。

[0068] 在这次洗涤之后，添加 Read Buffer T(Meso Scale Discovery) 以帮助检测结合的 SULFO-TAGTM 偶联检测抗体。当用电刺激微量板时，在读取缓冲液中共反应物三丙胺 (tripropylamine，TPA) 的存在下，SULFO-TAGTM 标记在 620nm 下发射光。所发射的光量与初始步骤中捕捉抗体所结合的 AMG 139 的量成比例。使用适当的板读取器，例如配备有 DiscoveryWorkbench 软件的 Sector Imager 6000 检测发光。使用 Watson 实验室信息管理系统数据缩减包，使用加权因子为 1/Y2 的 5PL（自动估计）(5 参数逻辑斯蒂 (5-parameter logistic)) 回归模型来缩减数据。通过与标准品和质量对照样品形成的标准曲线相比较来测定给定血清样品中 AMG 139 的量。

[0069] 在 A 部分中，如在除 7mg SC 剂量外的所有测试剂量中血清 AMG 139 的暴露量大致随剂量成比例增加所指示，健康受试者 (n ＝ 42) 的 AMG 139 血清浓度与时间曲线展现出线性 PK（图 1 和图 2)。在单次 SC 施用之后，所有剂量的中值 T_{max} 值在 4 到 8 天的范围内（表 2)。据估计，在单次 SC 剂量之后的相对生物利用率是 68.9％。对于所有剂量水平，在 SC 或

IV 施用之后，终末半衰期的组平均估计值在 26.6 到 33.0 天的范围内，这是 IgG 抗体典型的。

[0070] 在 B 部分中，如本研究中测试的所有剂量中血清 AMG 139 的暴露量大致随剂量成比例增加所指示，患有 PsO 的受试者 (n = 12) 的 AMG 139 血清浓度与时间曲线展现出线性 PK(图 3 和图 4)。在单次 SC 施用之后，所有剂量的中值 T_{max} 值在 9 到 13 天的范围内 (表 1)。据估计，在单次 SC 或 IV 剂量之后的相对生物利用率是 66.9％。对于所有剂量水平，在 SC 或 IV 施用之后，终末半衰期的组平均估计值在 21.6 到 31.0 天的范围内，这是 IgG 抗体典型的。

[0071] 总的说来，A 部分中的健康受试者与 B 部分中患 PsO 的受试者之间的 AMG 139 PK 是相似的。一个例外是，健康受试者显示出比患有 PsO 的受试者高的 AMG 139 暴露量 (AUC 和 C_{max})。在 SC 施用之后，中值 T_{max} 在健康受试者中比在患有 PsO 的受试者中早出现。健康受试者与患有 PsO 的受试者的平均 AMG 139 半衰期值 (分别是 26.6 到 33.0 天与 21.6 到 31.0 天) 以及生物利用率 (分别是 68.9％与 66.9％) 是类似的。在健康受试者 (A 部分) 间和在患有 PsO 的受试者 (B 部分) 间，AMG 139 的清除率 (CL) 和分布容积 (V_z) 对于所有剂量水平是一致的。

[0072] 另外测试患者样品中抗体与 AMG 139 的结合。该检验利用了电化学发光 (electrochemiluminescence，ECL)MSD(Meso Scale Discovery) 技术平台，该技术平台是基于抗体结合的多价特征。测试策略涉及一种分层的双检验方法，该方法由筛选检验和特异性检验组成。在特异性检验中，通过在测试前将样品与过量 AMG 139 一起温育来进一步测试在筛选检验中信噪比 (S/N) 高于检验截止点的样品。

[0073] 为了能解离抗体复合物，在分析之前对样品进行酸处理。将酸处理过的血清样品和对照物添加到由含等量生物素化 AMG 139(B-AMG 139) 和钌化 AMG 139(Ru-AMG 139) 的 1M Tris(pH 9.5) 组成的溶液中，并在环境温度下温育以使抗 AMG 139 抗体结合 B-AMG 139 分子和 Ru-AMG 139 分子，由此形成复合物。

[0074] 温育之后，将所有样品和对照物转移到经过洗涤的涂有抗生蛋白链菌素的标准结合 MSD 板中，用牛血清白蛋白阻断，并在环境温度下温育以允许捕捉 B-AMG 139 和在抗生蛋白链菌素表面上形成的复合物。洗涤板孔，并且添加含三丙胺的 MSD 读取缓冲溶液。在 MSD Sector Imager 6000 板读取器上读取板。在该仪器内，钌参与在施加电压时触发的电化学发光反应。被捕捉在板孔上的含 Ru-AMG 139 的复合物产生的 ECL 信号与样品中抗 AMG 139 抗体的浓度成比例。

[0075] 在本研究中，73 位受试者都未产生抗药物抗体。因此，无法评估免疫原性对 AMG 139 配置的可能影响。

[0076] 表 2 :在 SC 或 IV 施用单次剂量之后，健康受试者 (A 部分) 和患有 PsO 的受试者 (B 部分) 中 AMG 139 的平均 PK 参数，研究 20080767

[0077]

途径	剂量 (mg)	N	C_{max} (μg/mL)	t_{max} (天)	AUC_{last} (天 •μg/mL)	AUC_{inf} (天 •μg/mL)	$t_{1/2,z}$ (天)	CL^a (mL/天)	V_Z^a (L)
A 部分（健康受试者）									
SC	7	6	0.581(20.0)	6.0(1.0-21)	26.4(28.2)	28.9(29.6)	30.3(13.0)	256(22.9)	11.1(22.1)
	21	6	1.72(33.7)	8.0(4.0-14)	71.7(17.3)	76.2(16.5)	26.6(11.3)	282(15.9)	10.8(21.0)
	70	6	7.79(23.4)	8.0(7.8-8.2)	341(32.9)	373(35.2)	29.0(21.0)	218(51.3)	8.34(20.5)
	210	6	24.3(22.2)	4.0(3.9-10)	940(28.9)	1008(27.6)	27.8(12.3)	223(30.0)	8.83(26.3)
IV	210	6	73.0(20.4)	0.17(0.17-0.33)	1430(22.7)	1471(20.8)	28.4(11.1)	147(18.0)	5.98(15.9)
	420	6	122(14.9)	0.17(0.063-0.17)	2109(24.1)	2453(13.7)	33.0(5.6)	174(13.3)	8.25(11.3)
	700	6	175(16.8)	0.17(0.042-0.33)	3705(17.6)	3801(17.8)	32.9(10.9)	188(15.0)	8.93(18.3)
B 部分（患有 PsO 的受试者）									
SC	21	3	1.23(18.1)	13(6.0-13)	62.2(4.5)	67.8(4.9)	29.9(10.6)	310(4.8)	13.4(9.8)
	70	3	5.43(21.6)	10(6.0-10)	200(38.6)	207(40.6)	21.6(15.6)	376(38.0)	11.4(29.1)
	210	3	13.7(14.5)	9.0(4.0-9.9)	630(20.2)	637(20.3)	25.6(11.3)	338(18.2)	12.4(19.2)
IV	700	3	157(17.6)	0.17(0.057-0.33)	3101(17.6)	3138(18.0)	31.0(8.1)	229(20.1)	10.2(16.2)

[0078] AUC_{inf}＝从时间 0 到无穷大的浓度－时间曲线下面积；AUC_{last}＝从时间 0 到最后一个可测量浓度的时间的浓度－时间曲线下面积；CL ＝清除率；C_{max}＝给药后所观察到的最大浓度；% CV ＝变异系数；F ＝生物利用率；IV ＝静脉内；PsO ＝银屑病；SC ＝皮下；$t_{1/2,z}$＝消除半衰期；t_{max}＝达到所观察的最大浓度的时间；V_z＝分布容积；V_z/F ＝表观分布容积

[0079] PK 参数是以具有 3 个有效数字的平均值 (CV%) 报导，不过 t_{max}除外，它是以四舍五入到 2 个有效数字的中值 (min-max) 报导。% CV 精确到 1 个小数位。

[0080] [a]CL 和 V_z对于 SC 施用来说，表示 CL/F 和 V_z/F。

[0081] 实施例 2

[0082] 在先前提到的 1a 期 FIH 研究 (20080767,B 部分) 中，评价 AMG 139 在患有 PsO 的受试者中的功效作为第二终点。与安慰剂组相比较，在所有 AMG 139 治疗组中都出现平均银屑病皮损面积和严重程度指数 (PASI) 评分 (图 5 和图 6，以及表 3)、平均靶病变评分以及平均医师整体评估 (PGA) 的减小。即使每个治疗组中受试者的数量较少，但很明显，就接受低至 70mg SC 剂量的治疗组中反应的程度和持续时间来说，单次施用 AMG 139 是有效的。从治疗组中随时间达到 PASI 50、PASI 75 或 PASI 90 的受试者的数量和百分比，以及在研究期间的任何时间治疗组中达到 PASI 50、PASI 75、PASI 90 或 PASI 100 的受试者的数量和百分比也显而易见功效。对于任何给定剂量，治疗作用 (PASI、靶病变评分、PGA) 看来在约第 85 天到第 113 天达到其最大值。PASI 评分相对于基线的平均变化百分比高达约 90% (即，在第 85 天、第 113 天和第 169 天，AMG 139210mg SC 组)。AMG 139210mg SC 组和 700mg IV 组在第 113 天的结果表明，由单次剂量引起的 AMG 139 的治疗作用在约第 169 天之后开始返回基线水平。根据 AMG 139 的组平均终末半衰期值主要在 25 到 30 天的范围内，对于任何给定剂量，到第 169 天时 AMG 139 的循环含量是约 1% 到 2% 的 C_{max}。另外，在各种时间点获取受试者和受试者病变的照片。总的说来，这些照片在视觉上以及质量上都与 PASI、靶病变评估及 PGA 结果一致。

[0083] 表 3 :有关在研究 (B 部分 :研究 20080767) 期间的任何时间达到 PASI 50、PASI 75、PASI 90 或 PASI 100 的受试者的概述

[0084]

	治疗组

[0085]

PASI 反应	安慰剂 B 部分 N = 5 n (%)	B1 组 21 mg SC N = 3 n (%)	B2 组 70 mg SC N = 3 n (%)	B3 组 210 mg SC N = 3 n (%)	B4 组 700 mg IV N = 3 n (%)
PASI 50	2 (40)	3 (100)	3 (100)	3 (100)	3 (100)
PASI 75	0 (0)	1 (33)	3 (100)	3 (100)	2 (67)
PASI 90	0 (0)	1 (33)	1 (33)	2 (67)	1 (33)
PASI 100	0 (0)	0 (0)	0 (0)	2 (67)	0 (0)

[0086] IV = 静脉内 ;N = 具有基线 PASI 评分的受试者的数量 ;PASI = 银屑病活动性和严重程度指数 ;SC = 皮下

[0087] 实施例 3

[0088] 建立 AMG 139 的定量种群药物动力学 (quantitative population pharmacokinetics,pop PK) 模型以模拟未来给药方案的 PK,并且结合定量 PK/ 药效学模型以模拟 AMG 139 功效。pop PK 模型是基于以上所描述的健康受试者和 PsO 患者的数据。

[0089] 皮下剂量 (SC ;7mg、21mg、70mg 或 210mg) 或静脉内剂量 (IV ;210mg、420mg 或 700mg) 的 pop PK 模型是用 NONMEMv7.2 建立。数据分析使用个别 PK 数据同时拟合结构双房室模型,其中一级消除来自中央房室并且一级吸收来自储存房室 (depot compartment) (图 7)。对受试者间变化参数和残余误差模型进行改变以获得最低目标函数。研究体重和疾病作为潜在的 PK 协变量。

[0090] 最终的 AMG 139 pop PK 模型预测出平均浓度 - 时间曲线,该曲线在 90% 置信区间内数据拟合良好 (图 8) 并且目测预测诊断曲线显示出观测值与预测值之间的强相关性 (图 8 和图 9)。吸收速率常数、全身清除率 (CL) 和中央分布容积 (V_c) 分别是 0.242h^{-1}、0.171L/ 天及 3.58L,其中个体间变化率分别是 66%、24% 和 20% (表 4)。以体重作为协变量对于 CL 和 V_c 分别得到 1.04 和 1.11 的功率系数值,并且与 CL 和 V_c 显示正相关 (图 10)。在针对体重进行调整之后,疾病状态协变量对 CL 的额外影响 [1.13 倍增加 (0.93-1.3,95% CI)] 对于模型在这项 1 期研究数据集中未显示统计学显著的改善。

[0091] 表 4 :在向健康志愿者和银屑病受试者施用单次剂量 AMG 139 之后的种群 PK 模型参数估计

[0092]

参数	参数估计值	SE	个体间变化率（%）	SE
ka（hr^{-1}）	0.242	0.0354	66	9
CL（L/天）	0.171	0.0149	24	3
V_c（L）	3.58	0.318	20	2
V_p（L）	3.16	0.322	25	3
Q（L）	0.576	0.107	90	15

[0093] AMG 139 pop PK模型确定了在未来的发炎性疾病群体中模拟AMG 139 PK，以及结合正在进行的有关确立PK/药效学模型的功效研究的效用。

[0094] 这些结果支持了向罹患IL-23路径相关性银屑病的个体施用抗IL-23抗体的若干给药方案。适当给药方案可以选自下表5中所示的给药方案。

[0095] 表5：给药方案

[0096]

每1个月（0.5－1.5个月）21 mg SC或IV；21 mg包括在15－54 mg范围内的量
每3个月（1.5－4.5个月）70 mg SC或IV；70 mg包括在55－149 mg范围内的量
每6个月（4－8个月）210 mg SC或IV；210 mg包括在150－299 mg范围内的量
每6个月（4－12个月）700 mg SC或IV；700 mg包括在300－1100 mg范围内的量

[0097] 实施例4

[0098] 在本研究的A部分和B部分中，免疫表型分析是主要终点。通过对全血样品进行流式细胞术，随时间计算包括T细胞、B细胞、NK细胞、调控性T细胞（Treg）及Th17细胞在内的淋巴细胞群的数量。

[0099] 在指定时间点，从受试者采集全血放入含乙二胺四乙酸（EDTA）钾的玻璃管中，并且在24小时内（A1组-A7组）或在室温下温育24小时后进行处理（B1组-B4组）。使用CYTO-STAT tetraCHROME® 染色试剂盒（Beckman Coulter，Fullerton，CA）对T细胞群（CD3+、CD4+和CD8+）、B细胞群及NK细胞群进行计数。使用偶联荧光染料的单克隆抗体的定制组合，在独立管中鉴别其它T细胞群（Treg细胞和Th17细胞）。

[0100] 在对全血进行抗体染色之后，使用Coulter IMMUNOPREP试剂系统（Beckman Coulter）溶解所有样品中的红细胞，并将其固定于1％的多聚甲醛溶液中。对于针对T细胞、B细胞和NK细胞染色而带有标记物的血液，立即通过流式细胞术对样品进行分析。在通过流式细胞术进行分析之前，对针对Treg和Th17细胞群染色而带有标记物的血液进行洗涤。

[0101] 流式细胞术

[0102] 数据采集和分析是使用一种具有单一蓝光激光器（488nm）和五色光学配置的

FC500 流式细胞仪 (Beckman Coulter) 进行。初始的淋巴细胞门控是针对展现较低侧向散射特征的 CD45 表达群设置。T 细胞 (包括 Treg 和 Th17) 和 NK T 细胞群是源自于淋巴细胞的 CD3+ 子群。NK 细胞群和 B 细胞群是从淋巴细胞的非 CD3 表达子群鉴别得到。

[0103] CYTO-STAT tetraCHROME® 染色试剂盒 (Beckman Coulter) 允许使用 Flow-Count 荧光球 (Beckman Coulter),利用单一平台对 T 细胞、B 细胞、NK 细胞和 NK T 细胞进行计数 ;因此,这些细胞群是以绝对计数报导。Treg 细胞和 Th17 细胞是以占总 CD3+CD4+ 细胞的百分比报导,因为在这些测试中未纳入 Flow-Count 荧光球。这些细胞群的绝对计数可以使用每个登记的受试者在免疫表型分析当天的临床淋巴细胞计数计算。

[0104] 在 AMG 139 治疗的受试者中未观察到以上提到的淋巴细胞类型的数量或在体外刺激时表达以上提到的细胞因子的 CD4+ 或 CD8+ 淋巴细胞的频率的变向。在用 AMG 139 治疗 PsO 受试者之后,观察到较少的差别调控的基因 (病变 / 非病变),这与药物相关性 PD 效应一致。

[0001]

序列表

<110> AMGEN INC.
GIBBS, et al.

<120> 使用抗 IL-23 抗体治疗银屑病的方法

<130> 32053/47590 PC

<150> US-61/789,777
<151> 2013-03-15

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<170> PatentIn 3.5 版

<210> 1
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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
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20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[0002]

85 90 95

Ala Arg Asp Arg Gly Tyr Thr Ser Ser Trp Tyr Pro Asp Ala Phe Asp
100 105 110

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 2
<211> 111
<212> PRT
<213> 智人

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Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Thr Gly Ala Gly
20 25 30

Tyr Asp Val His Trp Tyr Gln Gln Val Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Ser Gly Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95

Leu Ser Gly Trp Val Phe Gly Gly Gly Thr Arg Leu Thr Val Leu
100 105 110

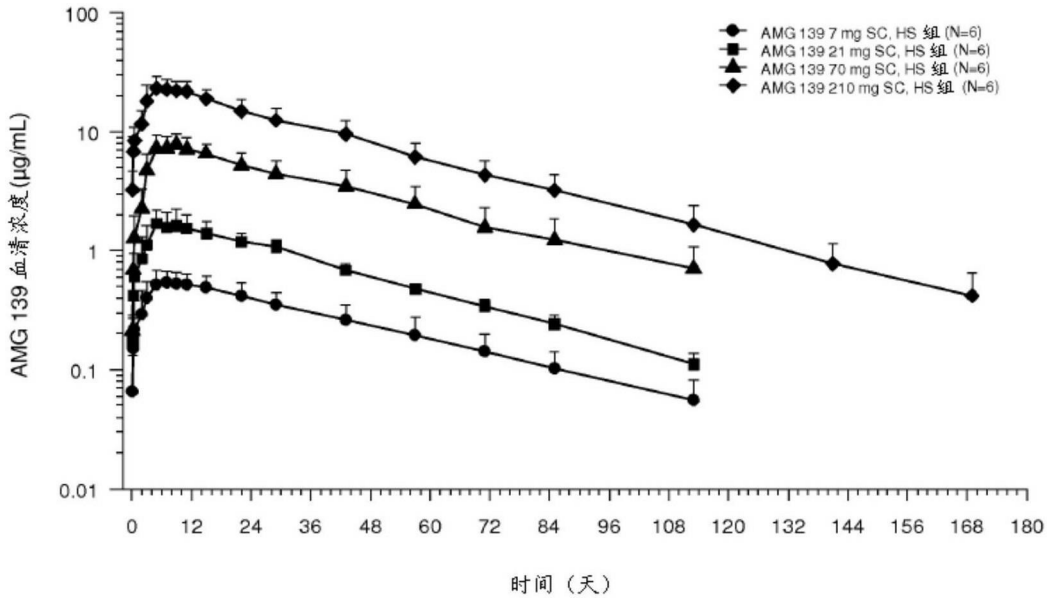
AMG 139 7 mg SC, HS 组 (N=6)
AMG 139 21 mg SC, HS 组 (N=6)
AMG 139 70 mg SC, HS 组 (N=6)
AMG 139 210 mg SC, HS 组 (N=6)
AMG 139 血清浓度 (μg/mL)
100
10
1
0.1
0.01
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180
时间（天）

图 1

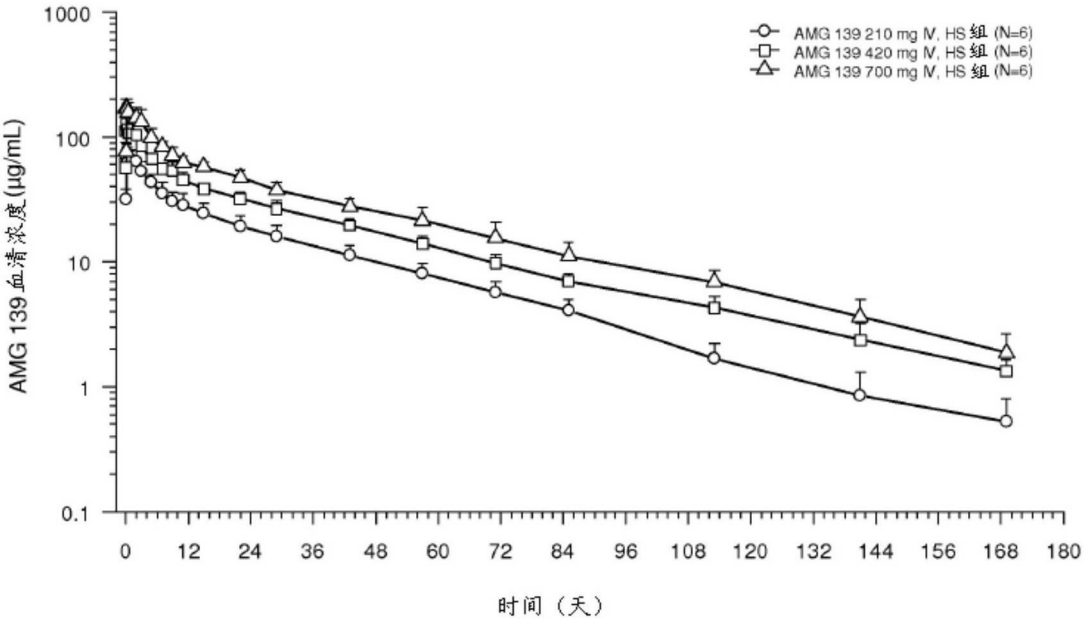
AMG 139 210 mg IV, HS 组 (N=6)
AMG 139 420 mg IV, HS 组 (N=6)
AMG 139 700 mg IV, HS 组 (N=6)
AMG 139 血清浓度 (μg/mL)
1000
100
10
1
0.1
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180
时间（天）

图 2

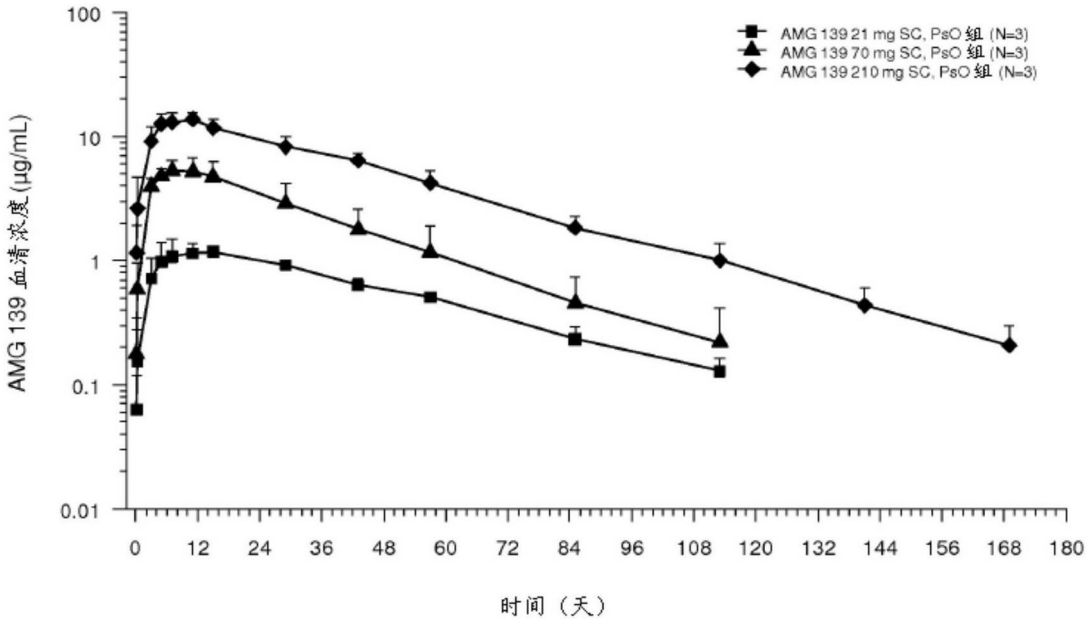
AMG 139 21 mg SC, PsO 组 (N=3)
AMG 139 70 mg SC, PsO 组 (N=3)
AMG 139 210 mg SC, PsO 组 (N=3)
AMG 139 血清浓度 (µg/mL)
100
10
1
0.1
0.01
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180
时间（天）

图 3

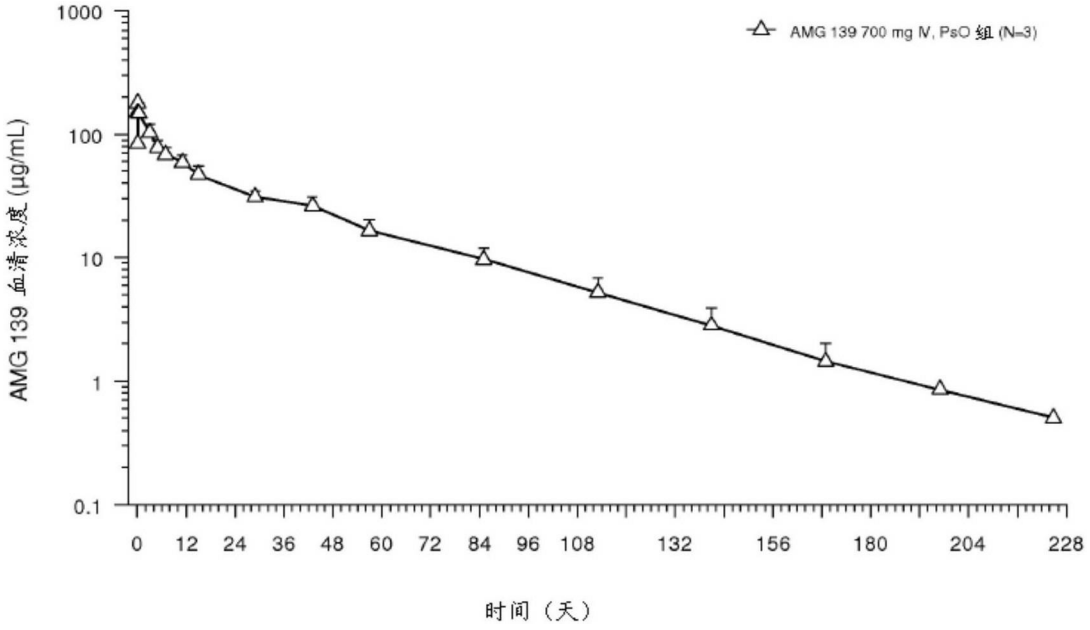
AMG 139 700 mg IV, PsO 组 (N=3)
AMG 139 血清浓度 (µg/mL)
1000
100
10
1
0.1
0 12 24 36 48 60 72 84 96 108 132 156 180 204 228
时间（天）

图 4

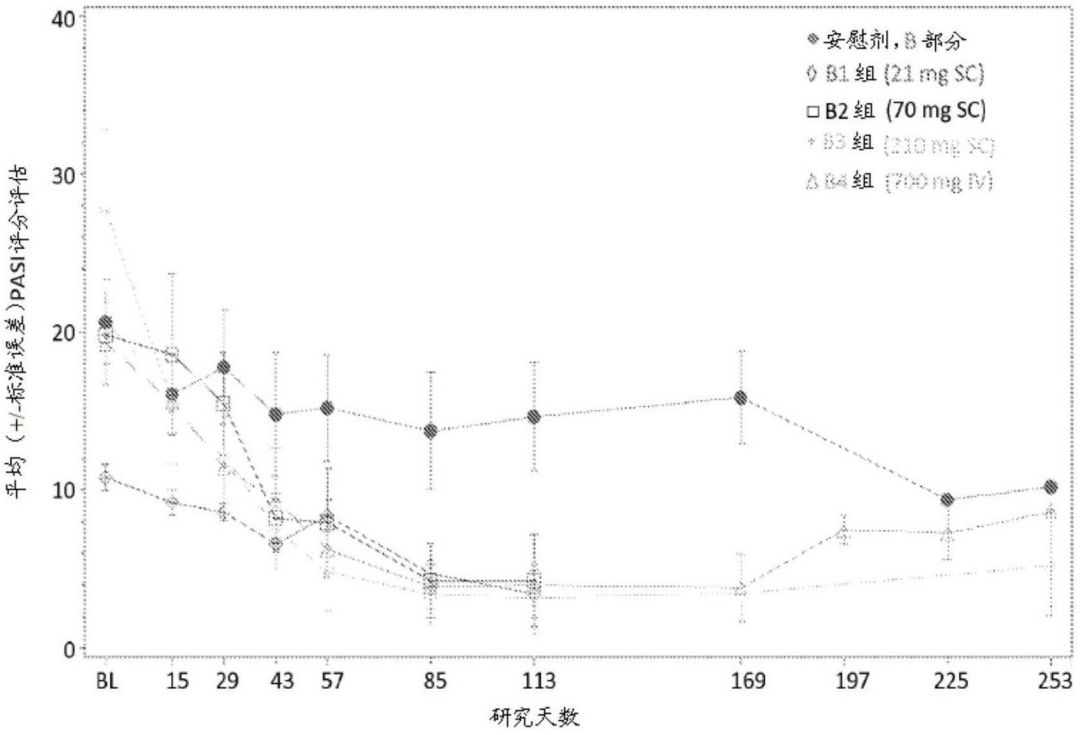
平均（+/-标准误差）PASI评分评估
40
30
20
10
0
BL
15
29
43
57
85
113
169
197
225
253
研究天数
安慰剂，B部分
B1组 (21 mg SC)
B2组 (70 mg SC)
B3组 (210 mg SC)
B4组 (700 mg IV)

图 5

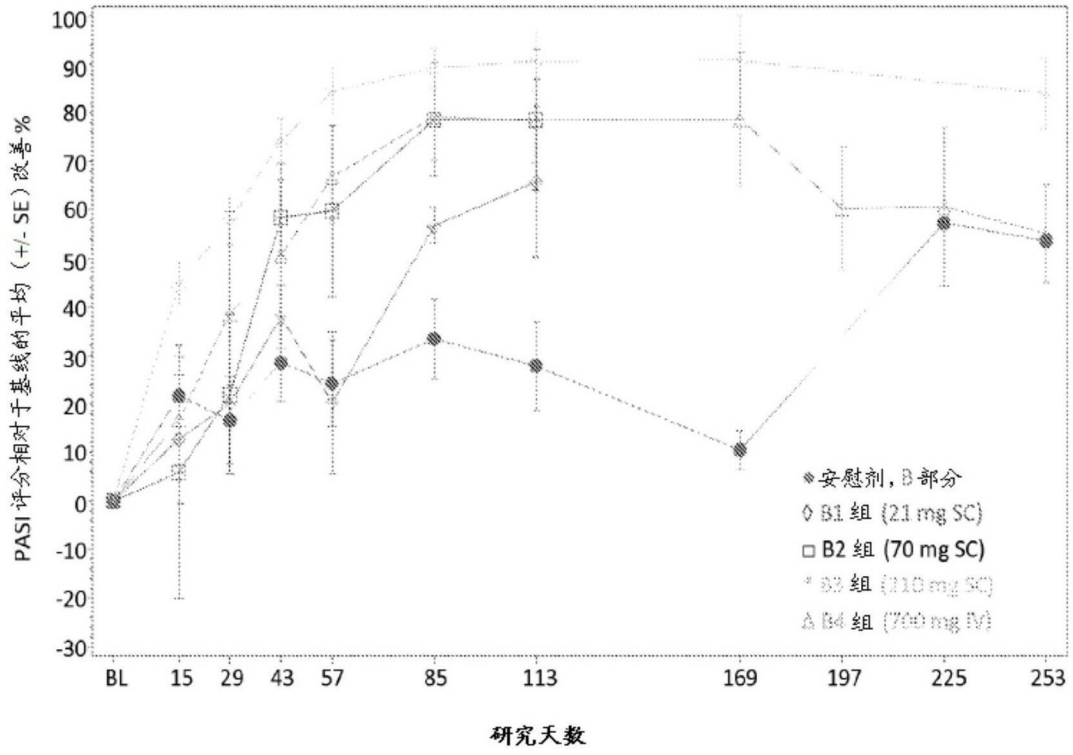
PASI评分相对于基线的平均（+/- SE）改善%
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
BL
15
29
43
57
85
113
169
197
225
253
研究天数
安慰剂，B部分
B1组 (21 mg SC)
B2组 (70 mg SC)
B3组 (210 mg SC)
B4组 (700 mg IV)

图 6

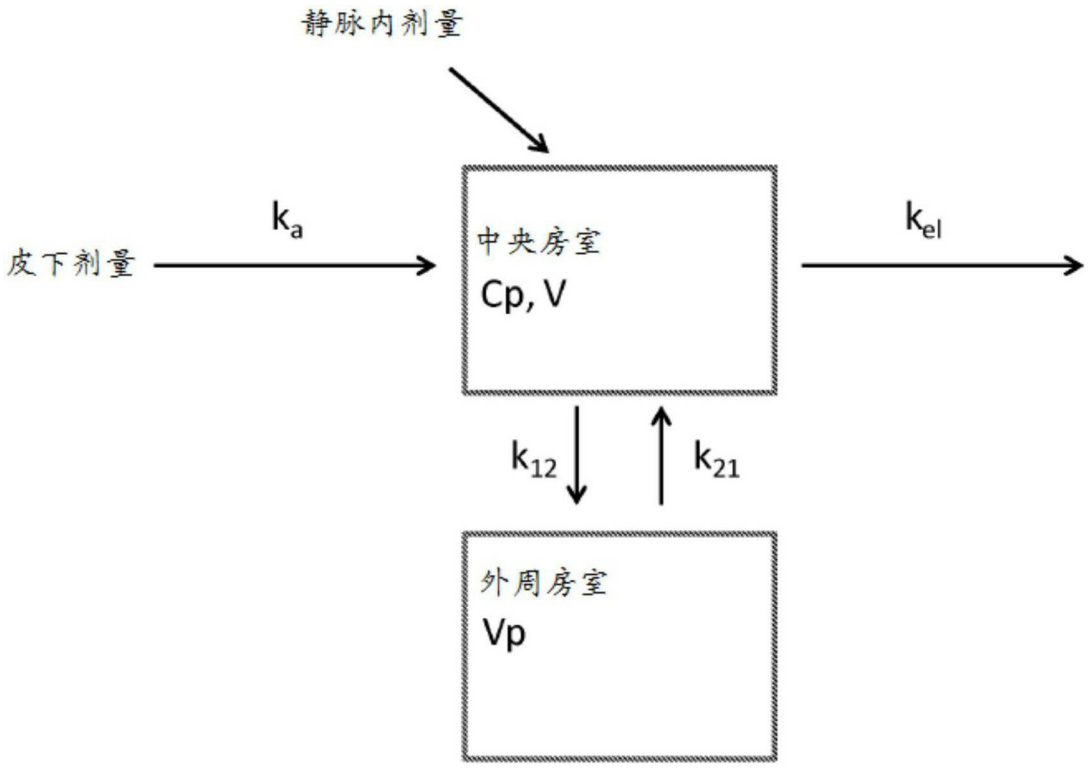

图 7

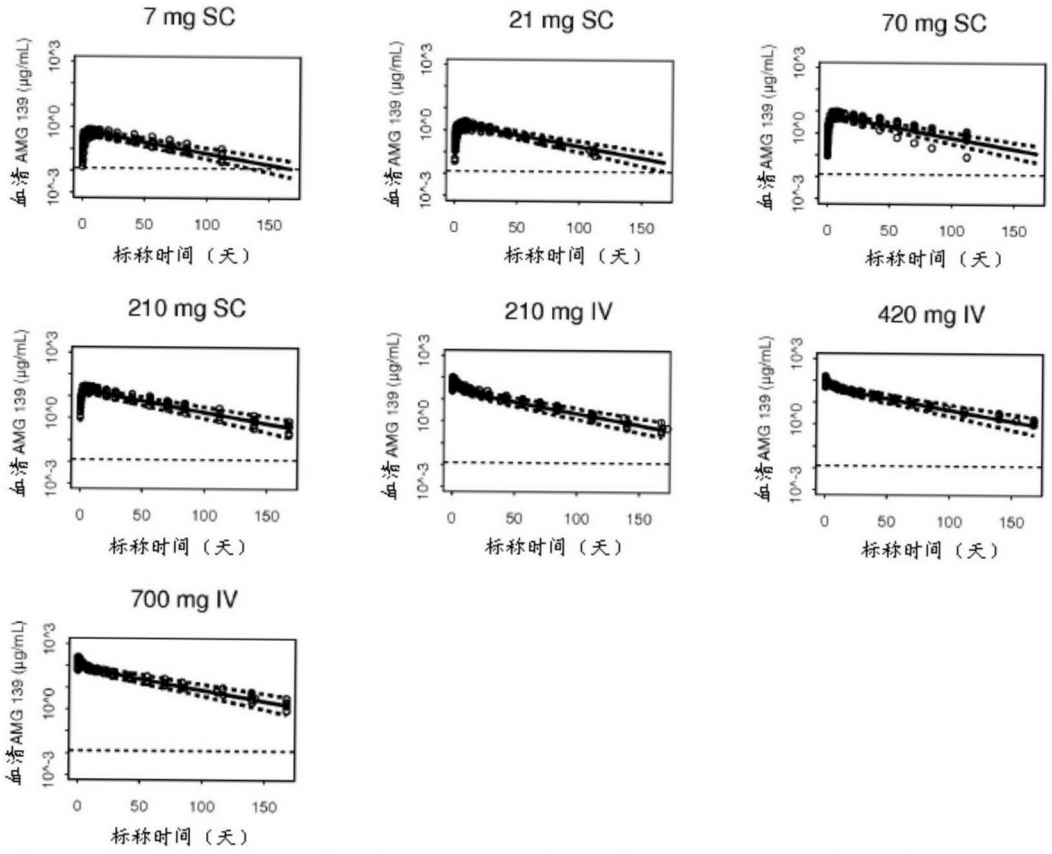
7 mg SC
21 mg SC
70 mg SC
210 mg SC
210 mg IV
420 mg IV
700 mg IV
血清AMG 139 (μg/mL)
10^3
10^0
10^-3
0
50
100
150
标称时间（天）

图 8

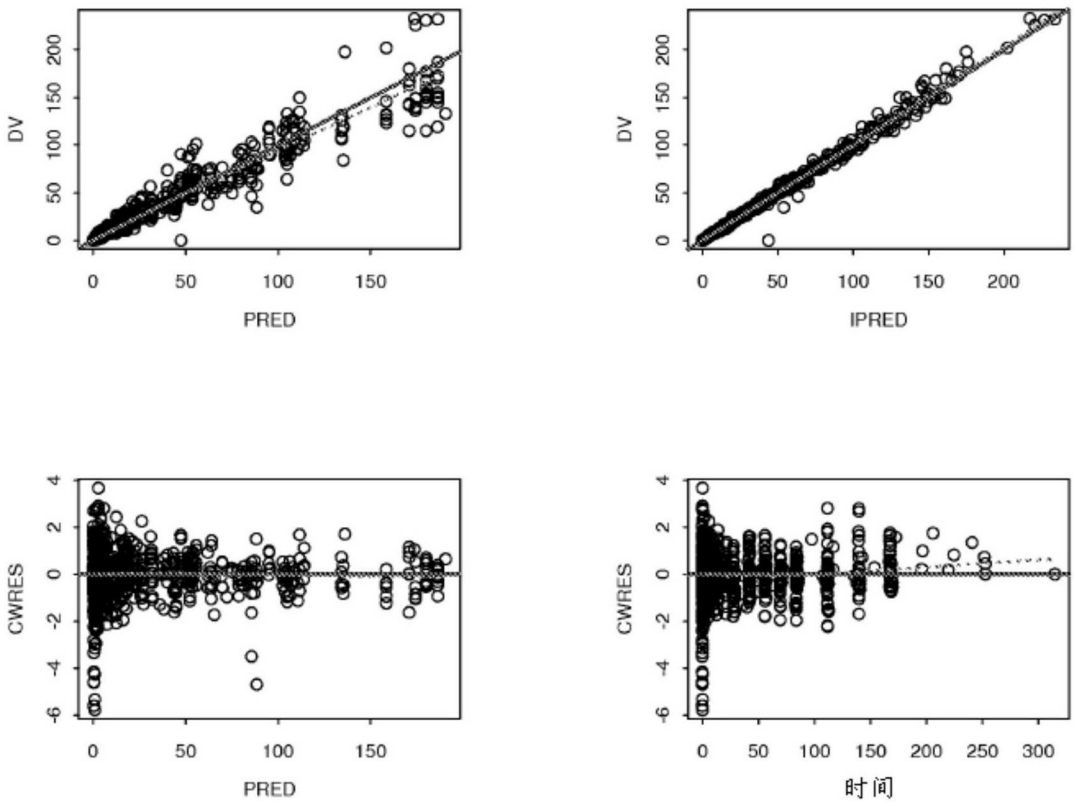

图 9

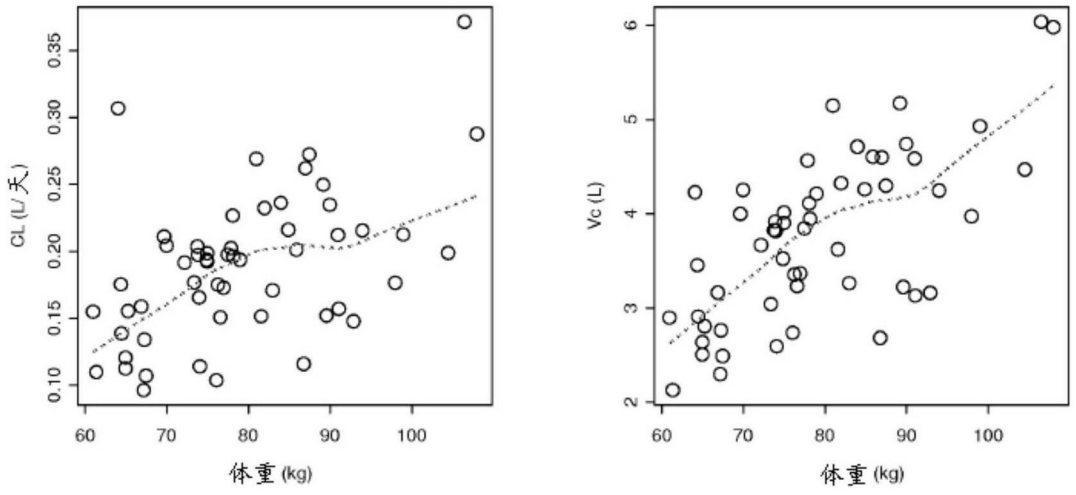

图 10

V_H1 (SEQ ID NO: 1)

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNEYYADSVKGR

CDR 1 CDR 2

FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGYTSSWYPDAFDIWGQGTMVTVSS

CDR 3

V_L1 (SEQ ID NO: 2)

QSVLTQPPSVSGAPGQRVTISCTGSSSNTGAGYDVHWYQQVPGTAPKLLIYGSGNRPS

CDR 1 CDR 2

GVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSGWVFGGGTRLTVL

CDR 3

图 11