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(54) **Title:** METHODS OF TREATING VASCULITIS USING AN IL-17 BINDING MOLECULE

(57) **Abstract:** The disclosure relates to a novel treatment of vasculitis, e.g., giant cell arteritis (GCA), polymyalgia rheumatica (PMR), Wegener's granulomatosis, polyarteritis nodosa, etc., which employs a therapeutically effective amount of an IL-17 binding molecule, e.g., an IL-17 antibody, such as the AIN457 (secukinumab) antibody, either alone or in combination (e.g., with ACZ885 (canakinumab)).



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METHODS OF TREATING VASCULITIS USING AN IL-17 BINDING MOLECULE

TECHNICAL FIELD

The disclosure relates to a novel treatment of vasculitis, e.g., giant cell arteritis (GCA), polymyalgia rheumatica (PMR), Wegener's granulomatosis, polyarteritis nodosa, etc., which employs a therapeutically effective amount of an IL-17 binding molecule, e.g., an IL-17 antibody, such as the AIN457 antibody.

BACKGROUND OF THE DISCLOSURE

Vasculitis (e.g., angiitis and arteritis) is an inflammation of the blood vessels (e.g., inflammation of medium, small, and large vessels). The inflammation induces changes in blood vessel walls, including thickening, weakening, narrowing, and scarring. Vasculitis can be primary (i.e., having unknown cause) or secondary (i.e., occurring as a result of another disorder). Secondary vasculitis may be found in conjunction with infection, immune disorders (e.g., lupus, rheumatoid arthritis, Sjogren's system), allergic reactions, and blood cell cancers (e.g., leukemia and lymphoma). Vasculitis may be acute or chronic, with severe forms resulting in ischemia, organ and tissue damage, and death.

Polymyalgia rheumatica (PMR) is a systemic inflammatory disorder that causes muscle pain and stiffness, primarily in the neck, shoulders, upper arms, hips and thighs in persons 50 years or older. (Gonzalez-Gay *et al.* (2010) Expert Opin. Pharmacother. 11:1077-87). The cause of PMR is not well understood, although various reports suggest an influence of inheritance, viral infection and/or autoantigens as possible triggers. (Ly *et al.* (2010) Autoimmunity Rev., May 8, 2010 e-published, PMID: 20457278). PMR often overlaps in symptoms and clinical laboratory parameters with giant cell arteritis (GCA), a systemic large vessel vasculitis that results in inflammation in the lining of arteries (most often arteries in the head and neck), in the elderly. (Chew *et al.* (2009) J. Clin. Neurosci. 16: 1263-68; Martinez-Taboada *et al.* (2008) Cytokine 44:207-220; Gonzalez-Gay *et al.*, *supra*). Morbidities associated with GCA include reduced blood

flow to the optic nerve and the brain, resulting in ischemic optic neuropathy leading to visual loss and large vessel stenoses leading to stroke. Other manifestations of GCA are extremity claudication and aortic aneurysm which can lead to aortic rupture, aortic dissection, and sudden death.

PMR and GCA may be a single pathophysiological disease spectrum or may be represent distinct conditions. (Miguel Gonzalez-Gay (2004) *Semin. Arthritis Rheum.* 33:289-293). PMR is two to three times more common than GCA, and PMR occurs in about 50 percent of patients with GCA, while only 15 to 30 percent of patients with PMR eventually develop GCA. (Salvarani et al. (2008) *Lancet* 372(9634):234-45). In temporal artery biopsies from PMR patients, overt inflammation and tissue destruction are typically absent by standard histological methods. However, recent reports in PMR patients reveal activated dendritic cells along the temporal artery adventitial-medial border, and low numbers of activated T cells and macrophages were detected by rt-PCR. Other evidence of ongoing inflammation in PMR temporal artery tissues includes detection of elevated mRNA levels for IL-1 β and IL-6. In sharp contrast to the granulomatous inflammation seen in temporal artery biopsies from GCA patients, IFN- γ producing T cells are not recruited into the vascular tissue in PMR. Moreover, while IFN- γ producing Th1 cells and IL-17-producing Th17 cells have been identified in early GCA, chronic GCA is characterized by persistent Th1-inducing signals, independent of IL-17-mediated inflammation (Weyand et al. (2011) *Current Opinion Rheumatol.* 23:43-49). Furthermore, the role of Th17 cells, and IL-17 in particular, during early and chronic PMR is unknown.

PMR and GCA are treated with oral corticosteroids, such as prednisone, prednisolone, methylprednisone, methylprednisolone, or deflazacort. (*see, e.g.,* Hernandez-Rodrigues *et al.* (2009) *Arch. Intern Med.* 169:1839-1849). The dose of corticosteroid used to treat GCA is much higher and for longer duration than that used to treat PMR, and intravenous steroids are occasionally used in GCA. Addition of oral or intramuscular methotrexate provides a glucocorticoid-sparing effect during the acute phase of PMR, while infliximab (anti-TNF alpha antibody) does not appear to provide value in co-treatment. (*Id.*). After several weeks of treatment, and depending on the symptoms and results of various tests, e.g., erythrocyte sedimentation rate (ESR) and a C-

reactive protein (CRP) tests, corticosteroid dosage is reduced. (*Id.*). However, most GCA patients and many PMR patients continue maintenance phase corticosteroid treatment for 2-3 years, and relapse is common. (*Id.*).

While corticosteroids improve the symptoms of PMR and can reduce the risk of blindness and stroke in GCA, long-term use of corticosteroids results in a number of serious side effects, including osteoporosis, infections, hypertension, high cholesterol, diabetes, peptic ulcers, cataracts, and depression or other disturbances in emotional well-being. Some studies of corticosteroid therapy of GCA have found morbidity associated with the therapy comparable in severity to the disease itself. (Nesher G et al. (1994) J. Rheumatol. 21:1283-1286). As a result of the danger of long-term use of corticosteroid treatment, there is a need to develop alternative therapies that do not induce these serious side effects.

Accordingly, herein is disclosed a novel treatment for vasculitis, e.g., giant cell arteritis (GCA), polymyalgia rheumatica (PMR), Wegener's granulomatosis, polyarteritis nodosa, etc., which employs a therapeutically effective amount of an IL-17 binding molecule, e.g., an IL-17 antibody, such as the AIN457 antibody disclosed in WO 2006/013107 (also published as US20090280131, which is hereby incorporated by reference in its entirety)).

SUMMARY OF THE DISCLOSURE

It is one object of the disclosure to provide a method of treating vasculitis, e.g., giant cell arteritis (GCA), polymyalgia rheumatica (PMR), Wegener's granulomatosis, polyarteritis nodosa, etc., which employs a therapeutically effective amount of an IL-17 binding molecule, e.g., an IL-17 antibody, such as the AIN457 antibody (which is also known as "secukinumab") .

It is another object of the disclosure to provide the use of a therapeutically effective amount of an IL-17 binding molecule, e.g., an IL-17 antibody, such as the AIN457 antibody, for the treatment of vasculitis, e.g., giant cell arteritis (GCA), polymyalgia rheumatica (PMR), Wegener's granulomatosis, polyarteritis nodosa, etc.

It is yet another object of the disclosure to provide a therapeutically effective amount of an IL-17 binding molecule, e.g., an IL-17 antibody, such as the AIN457 antibody, for the manufacture of a medicament for the treatment of vasculitis, e.g., giant cell arteritis (GCA), polymyalgia rheumatica (PMR), Wegener's granulomatosis, polyarteritis nodosa, etc.

Accordingly, provided herein is a method of treating vasculitis in a subject comprising, administering a therapeutically effective amount of an IL-17 binding molecule to a subject in need thereof, wherein said IL-17 binding molecule comprises

- a) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- b) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- c) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- d) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- e) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- f) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- g) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or
- h) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6.

Further provided herein is an IL-17 binding molecule for use in the treatment of vasculitis, wherein said IL-17 binding molecule comprises

- a) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- b) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- c) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- d) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- e) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- f) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- g) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or
- h) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6.

Further provided herein is the use of an IL-17 binding molecule for the preparation of a medicament for the treatment of vasculitis, wherein said IL-17 binding molecule comprises

- a) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- b) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;

- c) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- d) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- e) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- f) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- g) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or
- h) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6.

In some embodiments of the disclosed methods, IL-17 binding molecules or uses the IL-17 binding molecule is AIN457 (secukinumab). In further embodiments, the vasculitis is an autoimmune vasculitis or a large vessel vasculitis. In further embodiments, the vasculitis is isolated PMR. In further embodiments, the vasculitis is PMR associated with GCA. In further embodiments, the vasculitis is isolated GCA. In further embodiments, the vasculitis is GCA associated with PMR. In one embodiment, an additional agent for use in the disclosed methods or uses, or to be co-administered with a disclosed IL-17 binding molecule, is selected from the group consisting of prednisone, methotrexate, prednisolone, methylprednisone, methylprednisolone and deflazacort.

Disclosed herein is also a method of treating vasculitis in a subject in need thereof, comprising:

- a) selecting a subject on the basis of the subject having vasculitis; and

b) providing said subject with a therapeutically effective amount of an IL-17 binding molecule, wherein said IL-17 binding molecule comprises

- i) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- iii) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- v) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- vii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or
- viii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6,

wherein providing said a therapeutically effective amount of an IL-17 binding molecule to said subject results in treatment of vasculitis.

Disclosed herein is also an IL-17 binding molecule for use in the treatment of vasculitis, wherein said IL-17 binding molecule comprises,

- i) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;

- ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- iii) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- v) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- vii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or
- viii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;

said use comprising

- a) selecting a subject on the basis of the subject having vasculitis; and
- b) providing said subject with a therapeutically effective amount of said IL-17 binding molecule.

In some embodiments of the disclosed methods, IL-17 binding molecules or uses, the IL-17 binding molecule is AIN457 (secukinumab). In further embodiments, the vasculitis is an autoimmune vasculitis or a large vessel vasculitis. In further embodiments, the vasculitis is isolated PMR. In further embodiments, the vasculitis is PMR associated with GCA. In further embodiments, the vasculitis is isolated GCA. In further embodiments, the vasculitis is GCA associated with PMR. In one embodiment, an additional agent for use in the disclosed methods or uses, or to be co-administered with a

disclosed IL-17 binding molecule, is selected from the group consisting of prednisone, methotrexate, prednisolone, methylprednisone, methylprednisolone and deflazacort.

Disclosed herein is also a method of regulating the dose and/or frequency of providing an IL-17 binding molecule to a subject having vasculitis comprising: (a) measuring the concentration of one of the following in blood or tissue of the subject: free IL-17 protein, IL-17 mRNA, and/or Th17 cells; and (b) increasing the dose and/or frequency of the IL-17 binding molecule if the concentration is below a predetermined value and reducing the dose and/or frequency of the IL-17 binding molecule if the concentration is above a predetermined value, thereby regulating the dose and/or frequency of providing the IL-17 binding molecule to the subject.

Disclosed herein is also an IL-17 binding molecule for use in the treatment of vasculitis in a subject, said use comprising: (a) measuring the concentration of one of the following in blood or tissue of the subject: free IL-17 protein, IL-17 mRNA, and/or Th17 cells; and (b) increasing the dose and/or frequency of the IL-17 binding molecule if the concentration is below a predetermined value and reducing the dose and/or frequency of the IL-17 binding molecule if the concentration is above a predetermined value, thereby regulating the dose and/or frequency of providing the IL-17 binding molecule to the subject.

Disclosed herein is also a method of selecting a subject having vasculitis for therapy with an IL-17 binding molecule comprising: (a) measuring the concentration of one of the following in blood or tissue of the subject: free IL-17 protein (i.e., unbound by the IL-17 binding molecule), IL-17 mRNA, and/or Th17 cells; and (b) selecting the subject for said therapy if the concentration exceed a control value, thereby selecting a subject having vasculitis for therapy with an IL-17 binding molecule

In some embodiments of the above methods, IL-17 binding molecules and uses, the control value is obtained from a derived from a person known not to have vasculitis. In some embodiments of the disclosed methods, the IL-17 binding molecule is AIN457 (secukinumab). In further embodiments, the vasculitis is autoimmune vasculitis or a large vessel vasculitis. In further embodiments, the vasculitis is isolated PMR. In further embodiments, the vasculitis is PMR associated with GCA. In further embodiments, the vasculitis is isolated GCA. In further embodiments, the vasculitis is GCA associated

with PMR. In one embodiment, an additional agent for use in the disclosed methods or uses, or to be co-administered with a disclosed IL-17 binding molecule, is selected from the group consisting of prednisone, methotrexate, prednisolone, methylprednisone, methylprednisolone and deflazacort.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Clinical trial study design.

Figure 2. Individual patient PMR-AS scores at baseline and day 15 for the 3 treatment groups.

Figure 3. Heterogeneity in PMR-AS component responses for biologic treatment versus prednisone.

DETAILED DESCRIPTION OF THE DISCLOSURE

The term “comprising” encompasses “including” as well as “consisting” e.g. a composition “comprising” X may consist exclusively of X or may include something additional e.g. X + Y.

The term “about” in relation to a numerical value x means, for example, +/-10%.

The word “substantially” does not exclude “completely” e.g. a composition which is “substantially free” from Y may be completely free from Y. Where necessary, the word “substantially” may be omitted from the definition of the disclosure.

By “IL-17 binding molecule” is meant any molecule capable of binding to the human IL-17 antigen either alone or associated with other molecules. The binding reaction may be shown by standard methods (qualitative assays) including, for example, a binding assay, competition assay or a bioassay for determining the inhibition of IL-17 binding to its receptor or any kind of binding assays, with reference to a negative control test in which an antibody of unrelated specificity but of the same isotype, e.g. an anti-CD25 antibody, is used. Non-limiting examples of IL-17 binding molecules include antibodies as produced by B-cells or hybridomas and chimeric, CDR-grafted or human antibodies or any fragment thereof, e.g. F(ab')₂ and Fab fragments, as well as single chain or single domain antibodies.

The term "antibody" as referred to herein includes whole antibodies and any antigen binding fragment (i.e., "antigen-binding portion") or single chains thereof. A naturally occurring "antibody" is a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system.

The term "antigen binding site" of an antibody as used herein, refers to portions or fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., IL-17). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab)₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment (Ward et al., 1989 Nature 341:544-546), which consists of a VH domain; and an isolated complementarity determining region (CDR). Exemplary antigen binding sites include the CDRs of AIN457 as set forth in SEQ ID NOs:1-6 and 11-13.

Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic

linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see, e.g., Bird et al., 1988 Science 242:423-426; and Huston et al., 1988 Proc. Natl. Acad. Sci. 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen binding site" of an antibody. These antibody fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

The term "pharmaceutically acceptable" means a nontoxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s).

An "isolated antibody", as used herein, refers to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds IL-17 is substantially free of antibodies that specifically bind antigens other than IL-17). An isolated antibody that specifically binds IL-17 may, however, have cross-reactivity to other antigens, such as IL-17 molecules from other species. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

The term "human antibody", as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such human sequences, e.g., human germline sequences, or mutated versions of human germline sequences or antibody containing consensus framework sequences derived from human framework sequences analysis as described in Knappik, et al. (2000. J Mol Biol 296, 57-86). A "human antibody" need not be produced by a human, human tissue or human cell. The human antibodies of the disclosure may include amino acid residues not encoded by human sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo). However, the term "human antibody", as used herein, is not intended

to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

The term "IL-17" refers to IL-17A, formerly known as CTLA8, and includes wild-type IL-17A from various species (e.g., human, mouse, and monkey), polymorphic variants of IL-17A, and functional equivalents of IL-17A. Functional equivalents of IL-17A according to the present disclosure preferably have at least about 65%, 75%, 85%, 95%, 96%, 97%, 98%, or even 99% overall sequence identity with a wild-type IL-17A (e.g., human IL-17A), and substantially retain the ability to induce IL-6 production by human dermal fibroblasts.

The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, antibodies isolated from a recombinant, combinatorial human antibody library, and antibodies prepared, expressed, created or isolated by any other means that involve splicing of all or a portion of a human immunoglobulin gene, sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and

related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire in vivo.

As used herein, "isotype" refers to the antibody class (e.g., IgM, IgE, IgG such as IgG1 or IgG2) that is provided by the heavy chain constant region genes.

The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen".

The term " K_{assoc} " or " K_a ", as used herein, is intended to refer to the association rate of a particular antibody-antigen interaction, whereas the term " K_{dis} " or " K_D ," as used herein, is intended to refer to the dissociation rate of a particular antibody-antigen interaction. The term " K_D ", as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of K_d to K_a (i.e. K_d/K_a) and is expressed as a molar concentration (M). K_D values for antibodies can be determined using methods well established in the art. A method for determining the K_D of an antibody is by using surface plasmon resonance, or using a biosensor system such as a Biacore® system.

As used herein, the term "affinity" refers to the strength of interaction between antibody and antigen at single antigenic sites. Within each antigenic site, the variable region of the antibody "arm" interacts through weak non-covalent forces with antigen at numerous sites; the more interactions, the stronger the affinity. Standard assays to evaluate the binding affinity of the antibodies toward IL-17 of various species are known in the art, including for example, ELISAs, western blots and RIAs. The binding kinetics (e.g., binding affinity) of the antibodies also can be assessed by standard assays known in the art, such as by Biacore analysis. Assays to evaluate the effects of the antibodies on functional properties of IL-17 (e.g., receptor binding, preventing or ameliorating osteolysis) are described in further detail in the Examples.

As used herein, the term "cross-reactivity" refers to an antibody or population of antibodies binding to epitopes on other antigens. This can be caused either by low avidity or specificity of the antibody or by multiple distinct antigens having identical or very similar epitopes. Cross reactivity is sometimes desirable when one wants general binding to a related group of antigens or when attempting cross-species labeling when the antigen epitope sequence is not highly conserved in evolution.

As used herein, the term "subject" includes any human or nonhuman animal. The term "nonhuman animal" includes all vertebrates, e.g., mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows chickens, amphibians, reptiles, etc.

As used herein, the term, "optimized" means that a nucleotide sequence has been altered to encode an amino acid sequence using codons that are preferred in the production cell or organism, generally a eukaryotic cell, for example, a cell of *Pichia* or *Trichoderma*, a Chinese Hamster Ovary cell (CHO) or a human cell. The optimized nucleotide sequence is engineered to retain completely or as much as possible the amino acid sequence originally encoded by the starting nucleotide sequence, which is also known as the "parental" sequence. The amino acid sequences encoded by optimized nucleotide sequences are also referred to as optimized.

An antibody that "inhibits" one or more of these IL-17 functional properties (e.g., biochemical, immunochemical, cellular, physiological or other biological activities, or the like) as determined according to methodologies known to the art and described herein, will be understood to relate to a statistically significant decrease in the particular activity relative to that seen in the absence of the antibody (or when a control antibody of irrelevant specificity is present). An antibody that inhibits IL-17 activity effects a statistically significant decrease, e.g., by at least 10% of the measured parameter, by at least 50%, 80% or 90%, and in certain embodiments an antibody of the disclosure may inhibit greater than 95%, 98% or 99% of IL-17 functional activity.

The terms "cross-block", "cross-blocked" and "cross-blocking" are used interchangeably herein to mean the ability of an antibody or other binding agent to interfere with the binding of other antibodies or binding agents to IL-17 in a standard competitive binding assay. The ability or extent to which an antibody or other binding agent is able to interfere with the binding of another antibody or binding molecule to IL-17, and therefore whether it can be said to cross-block according to the disclosure, can be determined using standard competition binding assays. One suitable assay involves the use of the Biacore technology (e.g. by using the BIAcore® 3000 instrument (Biacore, Uppsala, Sweden)), which can measure the extent of interactions using surface plasmon

resonance technology. Another assay for measuring cross-blocking uses an ELISA-based approach.

For the purposes of the present description an antibody is “capable of inhibiting the binding of IL-17 to the same extent as AIN457” if the antibody is capable of inhibiting the binding of IL-17 to its receptor substantially to the same extent as the AIN457 antibody.

“Polypeptide“, if not otherwise specified herein, includes any peptide or protein comprising amino acids joined to each other by peptide bonds, having an amino acid sequence starting at the N-terminal extremity and ending at the C-terminal extremity.

A functional equivalent of a polypeptide includes a molecule having a qualitative biological activity in common with a polypeptide to the present disclosure, i.e. having the ability to bind to the human IL-17. A functional equivalent includes derivatives, fragments and peptide analogs of an IL-17 binding molecule according to the present disclosure. Fragments comprise regions within the sequence of a polypeptide according to the present disclosure, e.g., of a specified sequence.

The term "equivalent", unless otherwise indicated, is used to define amino acid sequence variants, and covalent modifications of an IL-17 binding molecule according to the present disclosure, e.g., of a specified sequence. The functional equivalents of an IL-17 binding molecule according to the present disclosure, e.g. of a specified sequence, such as the V_H and/or V_L sequences of AIN457 or the CDRs of AIN457, preferably have at least about 65%, 75%, 85%, 95%, 96%, 97%, 98%, or even 99% overall sequence identity with the specified sequence, and substantially retain the ability to bind the human IL-17 or, e.g., neutralize IL-6 production of IL-17 induced human dermal fibroblasts.

“Neutralize IL-6” as used herein refers to the ability of an IL-17 binding molecule to decrease IL-6 production from primary human dermal fibroblasts. The production of IL-6 in primary human (dermal) fibroblasts is dependent on IL-17 (Hwang SY et al., (2004) Arthritis Res Ther; 6:R120-128. In short, human dermal fibroblasts are stimulated with recombinant IL-17 in the presence of various concentrations of Antibody of the Disclosure or human IL-17 receptor with Fc part. The chimeric anti-CD25 antibody Simulect[®] (basiliximab) may be conveniently used as a negative control. Supernatant is taken after 16 h stimulation and assayed for IL-6 by ELISA. Antibodies of the Disclosure

typically have IC_{50} s for inhibition of IL-6 production (in the presence 1 nM human IL-17) of about 50 nM or less (e.g., from about 0.01 to about 50 nM) when tested as above, i.e. said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts. Preferably, the Antibodies of the Disclosure have an IC_{50} for inhibition of IL-6 production as defined above of about 20 nM or less, more preferably of about 10 nM or less, more preferably of about 5 nM or less, more preferably of about 2 nM or less, more preferably of about 1 nM or less.

The term "covalent modification" includes modifications of a polypeptide according to the present disclosure, e.g., of a specified sequence; or a fragment thereof with an organic proteinaceous or non-proteinaceous derivatizing agent, fusions to heterologous polypeptide sequences, and post-translational modifications. Covalent modified polypeptides, e.g., of a specified sequence, still have the ability to bind the human IL-17 or, e.g., neutralize IL-6 production of IL-17 induced human dermal fibroblasts by crosslinking. Covalent modifications are traditionally introduced by reacting targeted amino acid residues with an organic derivatizing agent that is capable of reacting with selected sides or terminal residues, or by harnessing mechanisms of post-translational modifications that function in selected recombinant host cells. Certain post-translational modifications are the result of the action of recombinant host cells on the expressed polypeptide. Glutaminyl and asparaginyl residues are frequently post-translationally deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deaminated under mildly acidic conditions. Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl, tyrosine or threonyl residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains, see, e.g., T. E. Creighton, *Proteins: Structure and Molecular Properties*, W. H. Freeman & Co., San Francisco, pp. 79-86 (1983). Covalent modifications, e.g., include fusion proteins comprising a polypeptide according to the present disclosure, e.g., of a specified sequence and their amino acid sequence variants, such as immunoadhesins, and N-terminal fusions to heterologous signal sequences.

As used herein, the term "stringent" describes conditions for hybridization and washing. Stringent conditions are known to those skilled in the art and can be found in

Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Aqueous and nonaqueous methods are described in that reference and either can be used. One example of stringent hybridization conditions is hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by at least one wash in 0.2X SSC, 0.1% SDS at 50°C. A second example of stringent hybridization conditions is hybridization in 6X SSC at about 45°C, followed by at least one wash in 0.2X SSC, 0.1% SDS at 55°C. Another example of stringent hybridization conditions is hybridization in 6X SSC at about 45°C, followed by at least one wash in 0.2X SSC, 0.1% SDS at 60°C. A further example of stringent hybridization conditions is hybridization in 6X SSC at about 45°C, followed by at least one wash in 0.2X SSC, 0.1% SDS at 65°C. High stringent conditions include hybridization in 0.5 M sodium phosphate, 7% SDS at 65°C, followed by at least one wash at 0.2X SSC, 1% SDS at 65°C.

The phrase "substantially as set out," "substantially identical" means that the relevant amino acid or nucleotide sequence (e.g., CDR(s), VH, or VL domain) will be identical to or have insubstantial differences (e.g., through conserved amino acid substitutions) in comparison to a particular reference sequence. Insubstantial differences include minor amino acid changes, such as 1 or 2 substitutions in a 5 amino acid sequence of a specified region. In the case of antibodies, the second antibody has the same specificity and has at least 50% of the affinity of the same.

Sequences substantially identical (e.g., at least about 85% sequence identity) to the sequences disclosed herein are also part of this application. In some embodiments, the sequence identity can be about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher. Alternatively, substantial identity exists when the nucleic acid segments will hybridize under selective hybridization conditions (e.g., highly stringent hybridization conditions), to the complement of the strand. The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form.

"Identity" with respect to a native polypeptide and its functional derivative is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues of a corresponding native polypeptide, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent identity, and not considering any conservative substitutions as part of the sequence identity.

Neither N- or C-terminal extensions nor insertions shall be construed as reducing identity. Methods and computer programs for the alignment are well known. The percent identity can be determined by standard alignment algorithms, for example, the Basic Local Alignment Tool (BLAST) described by Altshul et al. ((1990) J. Mol. Biol., 215: 403 410); the algorithm of Needleman et al. ((1970) J. Mol. Biol., 48: 444 453); or the algorithm of Meyers et al. ((1988) Comput. Appl. Biosci., 4: 11 17). A set of parameters may be the Blosum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5. The percent identity between two amino acid or nucleotide sequences can also be determined using the algorithm of E. Meyers and W. Miller ((1989) CABIOS, 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

"Amino acid(s)" refer to all naturally occurring L- α -amino acids, e.g., and including D-amino acids. The amino acids are identified by either the well known single-letter or three-letter designations.

The term "amino acid sequence variant" refers to molecules with some differences in their amino acid sequences as compared to a polypeptide according to the present disclosure, e.g., of a specified sequence. Amino acid sequence variants of a polypeptide according to the present disclosure, e.g., of a specified sequence, still have the ability to bind the human IL-17 or, e.g., neutralize IL-6 production of IL-17 induced human dermal fibroblasts. Substitutional variants are those that have at least one amino acid residue removed and a different amino acid inserted in its place at the same position in a polypeptide according to the present disclosure, e.g., of a specified sequence. These substitutions may be single, where only one amino acid in the molecule has been substituted, or they may be multiple, where two or more amino acids have been substituted in the same molecule. Insertional variants are those with one or more amino acids inserted immediately adjacent to an amino acid at a particular position in a polypeptide according to the present disclosure, e.g., of a specified sequence. Immediately adjacent to an amino acid means connected to either the α -carboxy or α -amino functional group of the amino acid. Deletional variants are those with one or more amino acids in a polypeptide according to the present disclosure, e.g., of a specified

sequence, removed. Ordinarily, deletional variants will have one or two amino acids deleted in a particular region of the molecule.

As used herein, a “therapeutically effective amount” refers to an amount of an IL-17 binding molecule (e.g., an IL-17 antibody, e.g., AIN457) that is effective, upon single or multiple dose administration to a subject (such as a human patient) at treating, preventing, curing, delaying, reducing the severity of, ameliorating at least one symptom of a disorder or recurring disorder, or prolonging the survival of the subject beyond that expected in the absence of such treatment. When applied to an individual active ingredient (e.g., an IL-17 binding molecule) administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In the present description the phrase “IL-17 mediated disease” encompasses all diseases and medical conditions in which IL-17 plays a role, whether directly or indirectly, in the disease or medical condition, including the causation, development, progress, persistence or pathology of the disease or condition.

In the present description the terms “treatment” or “treat” refer to both prophylactic or preventative treatment as well as curative or disease modifying treatment, including treatment of patient at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition, and includes suppression of clinical relapse. The treatment may be administered to a subject having a medical disorder or who ultimately may acquire the disorder, in order to prevent, cure, delay the onset of, reduce the severity of, or ameliorate one or more symptoms of a disorder or recurring disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

As used herein, the term “vasculitis” refers to an inflammation of a blood vessel (i.e., a vein or artery). Vasculitis may be acute or chronic, may be pauci-immune or immune, may be large (“large vessel vasculitis”) or small vessel (“small vessel vasculitis”), and may be primary or secondary to another disorder. Examples of vasculitis include, e.g., Behcet's syndrome, Buerger's disease (thromboangiitis obliterans), antineutrophil cytoplasmic autoantibody (ANCA)-associated systemic vasculitis (AASV), which

includes Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg–Strauss syndrome (CSS), cryoglobulinemia, giant cell arteritis (GCA), Henoch-Schonlein purpura, hypersensitivity vasculitis, Kawasaki disease (mucocutaneous lymph node syndrome), polyarteritis nodosa, rheumatoid vasculitis, Takayasu's arteritis, and polymyalgia rheumatica (PMR). Vasculitis, which includes autoimmune vasculitis, may be acute or chronic, and may be primary or secondary to another disorder. As used herein, the phrase “autoimmune vasculitis” refers to a vasculitis resulting from a subject's immune system reacting to a self antigen(s).

As used herein, “PMR” or “polymyalgia rheumatica” includes both isolated PMR and PMR associated with GCA. As used herein “isolated PMR” refers to PMR manifesting independently of GCA, e.g., PMR presenting individually at a different time than GCA or PMR presenting without any past manifestation of GCA or future development of GCA. As used herein “PMR associated with GCA” refers to PMR presenting concurrently with GCA. As used herein, “GCA” or “giant cell arteritis” (also sometimes referred to as “temporal arteritis”) includes both isolated GCA and GCA associated with PMR. As used herein “isolated GCA” refers to GCA manifesting independently of PMR, e.g., GCA presenting individually at a different time than PMR or GCA presenting without any past or future PMR manifestation. As used herein “GCA associated with PMR” refers to GCA presenting concurrently with PMR. A skilled clinician is capable of determining whether a particular subject is afflicted with PMR, GCA or both PMR and GCA using various tests, e.g., clinical manifestation, Healey criteria, AACR criteria, polymyalgia rheumatica activity score, vessel biopsy (e.g., temporal artery biopsy), blood tests such as a sedimentation rate, imaging, etc.

As used herein, the term “relapse” refers to the return of given symptoms or signs that had otherwise been abrogated or reduced due to a particular therapy, e.g., the return of muscle stiffness in a PMR patient following treatment or the return of an elevated sedimentation rate in a patient with PMR or GCA.

Various aspects of the disclosure are described in further detail in the following subsections.

IL-17 Binding Molecules

GCA is characterized by infiltrates of T lymphocytes, dendritic cells and macrophages in the walls of medium to large-sized arteries. (Salvarani et al. (2008) Lancet 372:234-45). These infiltrating cells produce various cytokines, chemokines, oxidative products, MMPs, and growth factors. The result is vascular and systemic inflammation followed by myointimal proliferation. The inflammation, the resulting swelling of the vessel wall, and the myointimal proliferation of the vessel can lead to luminal stenosis and ultimately occlusion and subsequent ischemia of the tissues supplied by the involved vessels. Recent reports indicate that IL-17-producing Th17 cells and the level of circulating IL-17 are increased in untreated GCA-patients, and that prednisone treatment decreases the proportion of Th17 cells, as well as levels of IL-17. (Deng et al. (2010) Circulation 121:906-915; Lopez-Hoyos et al. (2008) Arthritis Rheum;58:S392 (suppl)). Several reports indicate that PMR and GCA are characterized by increased circulating levels of IL-6, a non-specific inflammatory cytokine that can induce Th17 cells, and that corticosteroid treatment decreases IL-6 levels. (Martinez-Taboada et al, *supra*). However, there is disagreement in these studies between the correlation of the circulating IL-6 levels and parameters, such as the sedimentation rate and C-protein levels, that reflect the acute phase reaction of PMR. (*Id.*). While IL-17 and Th17 cells have yet to be reported present in PMR patients, the Th17 differentiation factors IL-6 and TGF- β have been detected in temporal artery biopsies (Weyand et al (1994) Ann Intern Med. 121:484-491) and circulating IL-6 levels are high in untreated patients (Martinez-Taboada et al, *supra*). A recently published *in vitro* study shows that IL-17 induces expression of the key PMR biomarker C-reactive protein (CRP) by Hep3B hepatocytes and coronary artery smooth muscle cells independently of IL-1 β and IL-6.

There is also evidence implicating IL-17 in other forms of vasculitis, such as Wegener's granulomatosis (Abdulahad WH et al. (2009) Nephrology 14:26-32). Current therapy for Wegener's granulomatosis and other forms of vasculitis utilizes strong immunosuppressant drugs with significant rates of adverse events, similar to what occurs with therapies for GCA.

Thus, the instant disclosure provides methods for treating vasculitis, e.g., giant cell arteritis (GCA) (GCA associated with PMR or isolated GCA), polymyalgia rheumatica (PMR) (PMR associated with GCA or isolated PMR), Wegener's granulomatosis, polyarteritis nodosa, etc., comprising administering a therapeutically effective amount of an IL-17 binding molecule, e.g., IL-17 antibodies, such as AIN457, to a subject having vasculitis.

In one embodiment, the IL-17 binding molecule comprises at least one immunoglobulin heavy chain variable domain (V_H) comprising in sequence hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:1 (N-Y-W-M-N), said CDR2 having the amino acid sequence SEQ ID NO:2 (A-I-N-Q-D-G-S-E-K-Y-Y-V-G-S-V-K-G), and said CDR3 having the amino acid sequence SEQ ID NO:3 (D-Y-Y-D-I-L-T-D-Y-Y-I-H-Y-W-Y-F-D-L); or direct CDR equivalents thereof.

In one embodiment, the IL-17 binding molecule comprises at least one immunoglobulin light chain variable domain (V_L) comprising in sequence hypervariable regions CDR1', CDR2' and CDR3', said CDR1' having the amino acid sequence SEQ ID NO:4 (R-A-S-Q-S-V-S-S-S-Y-L-A), said CDR2' having the amino acid sequence SEQ ID NO:5 (G-A-S-S-R-A-T) and said CDR3' having the amino acid sequence SEQ ID NO:6 (Q-Q-Y-G-S-S-P-C-T) or direct CDR' equivalents thereof.

In one embodiment, the IL-17 binding molecule comprises at least one immunoglobulin heavy chain variable domain (V_H) comprising in sequence hypervariable regions CDR1-x, CDR2-x and CDR3-x, said CDR1-x having the amino acid sequence SEQ ID NO:11 (G-F-T-F-S-N-Y-W-M-N), said CDR2-x having the amino acid sequence SEQ ID NO:12 (A-I-N-Q-D-G-S-E-K-Y-Y), and said CDR3-x having the amino acid sequence SEQ ID NO:13 (C-V-R-D-Y-Y-D-I-L-T-D-Y-Y-I-H-Y-W-Y-F-D-L-W-G); or direct CDR-x equivalents thereof.

In one embodiment, the IL-17 binding molecule comprises at least one immunoglobulin V_H domain and at least one immunoglobulin V_L domain, wherein:

- a) the immunoglobulin V_H domain comprises:
 - i. hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:1, said CDR2 having the

amino acid sequence SEQ ID NO:2, and said CDR3 having the amino acid sequence SEQ ID NO:3 or direct CDR equivalents thereof; or

ii. hypervariable regions CDR1-x, CDR2-x and CDR3-x, said CDR1-x having the amino acid sequence SEQ ID NO:11, said CDR2-x having the amino acid sequence SEQ ID NO:12, and said CDR3-x having the amino acid sequence SEQ ID NO:13 or direct CDR-x equivalents thereof; and

b) the immunoglobulin V_L domain comprises hypervariable regions CDR1', CDR2' and CDR3', said CDR1' having the amino acid sequence SEQ ID NO:4, said CDR2' having the amino acid sequence SEQ ID NO:5, and said CDR3' having the amino acid sequence SEQ ID NO:6 or direct CDR' equivalents thereof.

In one embodiment, the IL-17 binding molecule (e.g., IL-17 antibody, e.g., AIN457) comprises at least one immunoglobulin V_H domain and at least one immunoglobulin V_L domain, wherein:

a) the at least one immunoglobulin V_H domain comprises in sequence hypervariable regions CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:1, said CDR2 having the amino acid sequence SEQ ID NO:2, and said CDR3 having the amino acid sequence SEQ ID NO:3 or direct CDR equivalents thereof; and

b) the at least one immunoglobulin V_L domain comprises in sequence hypervariable regions CDR1', CDR2' and CDR3', said CDR1' having the amino acid sequence SEQ ID NO:4, said CDR2' having the amino acid sequence SEQ ID NO:5, and said CDR3' having the amino acid sequence SEQ ID NO:6 or direct CDR' equivalents thereof.

In one embodiment, the IL-17 binding molecule (e.g., IL-17 antibody, e.g., AIN457) comprises at least one immunoglobulin V_H domain and at least one immunoglobulin V_L domain, wherein:

a) the at least one immunoglobulin V_H domain comprises in sequence hypervariable regions CDR1-x, CDR2-x and CDR3-x, said CDR1-x having the

amino acid sequence SEQ ID NO:11, said CDR2-x having the amino acid sequence SEQ ID NO:12, and said CDR3-x having the amino acid sequence SEQ ID NO:13 or direct CDR-x equivalents thereof; and

b) the at least one immunoglobulin V_L domain comprises in sequence hypervariable regions CDR1', CDR2' and CDR3', said CDR1' having the amino acid sequence SEQ ID NO:4, said CDR2' having the amino acid sequence SEQ ID NO:5, and said CDR3' having the amino acid sequence SEQ ID NO:6 or direct CDR' equivalents thereof.

In one embodiment, the IL-17 binding molecule (e.g., IL-17 antibody, e.g., AIN457) comprises

- a) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- b) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- c) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- d) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- e) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- f) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- g) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or
- h) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6.

For ease of reference the amino acid sequences of the hypervariable regions of the AIN457 monoclonal antibodies, based on the Kabat definition and as determined by the X-ray analysis, using the approach of Chothia and coworkers, is provided in Table 1, below.

Light-chain		
CDR1'	Kabat definition	R-A-S-Q-S-V-S-S-S-Y-L-A (SEQ ID NO:4)
	Chothia/ X-ray definition	R-A- S-Q-S-V-S-S-S -Y-L-A (SEQ ID NO:4)
CDR2'	Kabat definition	G-A-S-S-R-A-T (SEQ ID NO:5)
	Chothia/ X-ray definition	G-A-S -S-R-A-T (SEQ ID NO:5)
CDR3'	Kabat definition	Q-Q-Y-G-S-S-P-C-T (SEQ ID NO:6)
	Chothia/ X-ray definition	Q-Q- Y-G-S-S-P-C -T (SEQ ID NO:6)
Heavy-chain		
CDR1	Kabat definition	N-Y-W-M-N (SEQ ID NO:1)
CDR1-x	Chothia/ X-ray definition	G-F-T-F-S-N -Y-W-M-N (SEQ ID NO:11)
CDR2	Kabat definition	A-I-N-Q-D-G-S-E-K-Y-Y-V-G-S-V-K-G (SEQ ID NO:2)
CDR2-x	Chothia/ X-ray definition	A-I- N-Q-D-G-S -E-K-Y-Y (SEQ ID NO:12)
CDR3	Kabat definition	D-Y-Y-D-I-L-T-D-Y-Y-I-H-Y-W-Y-F-D-L

		(SEQ ID NO:3)
CDR3-x	Chothia/ X-ray definition	C-V-R- D-Y-Y-D-I-L-T-D-Y-Y-I-H-Y-W-Y-F-D-L - W-G (SEQ ID NO:13)

Table 1 : Amino acid sequences of the hypervariable regions of the AIN457 monoclonal antibodies.

Amino acid highlighted in bold are part of the CDR loops, while those shown in plain style are part of the antibody framework.

Particularly preferred IL-17 binding molecules of the disclosure are human antibodies, especially the AIN457 antibody (secukinumab) as described in Examples 1 and 2 of WO 2006/013107. AIN457 is a high-affinity, fully human monoclonal anti-human interleukin-17A (IL-17A, IL-17) antibody of the IgG1/kappa isotype that is currently in clinical trials for the treatment of immune-mediated inflammatory conditions. The AIN457 antibody has binding affinity for IL-17 that is higher than affinities previously reported for anti-human IL-17 antibodies. AIN457 binds with very high affinity to recombinant human IL-17 (huIL-17); the K_D is about 200 pM (BIAcore®) (see, e.g., WO2006/013107 and WO2007/117749) and neutralizes human IL-6 production induced by huIL-17 in human dermal fibroblast with an IC_{50} is 2.1 ± 0.1 nM at a concentration of 1.87 nM huIL-17. Thus, AIN457 neutralizes antigen at a molar ratio of about 1:1. This high binding affinity makes the AIN457 antibody particularly suitable for therapeutic applications.

In preferred embodiments, the variable domains of both heavy and light chains are of human origin, for instance those of the AIN457 antibody which are shown in SEQ ID NO:10 (= variable domain of light chain, i.e., amino acid 1 to 109 of SEQ ID NO:10) and SEQ ID NO:8 (= variable domain of heavy chain, i.e., amino acid 1 to 127 of SEQ ID NO:8). The constant region domains preferably also comprise suitable human constant region domains, for instance as described in "Sequences of Proteins of Immunological Interest", Kabat E.A. et al, US Department of Health and Human Services, Public Health Service, National Institute of Health.

In some embodiments, an IL-17 binding molecule of the disclosure comprises the variable light domain of SEQ ID NO:10. In other embodiments, an IL-17 binding molecule of the disclosure comprises the variable heavy domain of SEQ ID NO:8. In other embodiments, an IL-17 binding molecule of the disclosure comprises the variable light domain of SEQ ID NO:10 and the variable heavy domain of SEQ ID NO:8. In some embodiments, an IL-17 binding molecule of the disclosure comprises the three CDRs of SEQ ID NO:10. In other embodiments, an IL-17 binding molecule of the disclosure comprises the three CDRs of SEQ ID NO:8. In other embodiments, an IL-17 binding molecule of the disclosure comprises the three CDRs of SEQ ID NO:10 and the three CDRs of SEQ ID NO:8. The CDRs of SEQ ID NO:8 and SEQ ID NO:10, according to both the Chothia and Kabat definition, may be found in **Table 1**, supra.

In some embodiments, an IL-17 binding molecule of the disclosure comprises the light domain of SEQ ID NO:15. In other embodiments, an IL-17 binding molecule of the disclosure comprises the heavy domain of SEQ ID NO:17. In other embodiments, an IL-17 binding molecule of the disclosure comprises the light domain of SEQ ID NO:15 and the heavy domain of SEQ ID NO:17. In some embodiments, an IL-17 binding molecule of the disclosure comprises the three CDRs of SEQ ID NO:15. In other embodiments, an IL-17 binding molecule of the disclosure comprises the three CDRs of SEQ ID NO:17. In other embodiments, an IL-17 binding molecule of the disclosure comprises the three CDRs of SEQ ID NO:15 and the three CDRs of SEQ ID NO:17. The CDRs of SEQ ID NO:15 and SEQ ID NO:17, according to both the Chothia and Kabat definition, may be found in **Table 1**, supra.

Hypervariable regions may be associated with any kind of framework regions, though preferably are of human origin. Suitable framework regions are described in Kabat E.A. et al, *ibid*. The preferred heavy chain framework is a human heavy chain framework, for instance that of the AIN457 antibody. It consists in sequence, e.g. of FR1 (amino acid 1 to 30 of SEQ ID NO:8), FR2 (amino acid 36 to 49 of SEQ ID NO:8), FR3 (amino acid 67 to 98 of SEQ ID NO:8) and FR4 (amino acid 117 to 127 of SEQ ID NO:8) regions. Taking into consideration the determined hypervariable regions of AIN457 by X-ray analysis, another preferred heavy chain framework consists in sequence of FR1-x (amino acid 1 to 25 of SEQ ID NO:8), FR2-x (amino acid 36 to 49 of

SEQ ID NO:8), FR3-x (amino acid 61 to 95 of SEQ ID NO:8) and FR4 (amino acid 119 to 127 of SEQ ID NO:8) regions. In a similar manner, the light chain framework consists, in sequence, of FR1' (amino acid 1 to 23 of SEQ ID NO:10), FR2' (amino acid 36 to 50 of SEQ ID NO:10), FR3' (amino acid 58 to 89 of SEQ ID NO:10) and FR4' (amino acid 99 to 109 of SEQ ID NO:10) regions.

In one embodiment, an IL-17 binding molecule (e.g., IL-17 antibody, e.g., AIN457) is selected from a human anti IL-17 antibody which comprises at least:

a) an immunoglobulin heavy chain or fragment thereof which comprises a variable domain comprising in sequence the hypervariable regions CDR1, CDR2 and CDR3 or direct CDR equivalents thereof and the constant part or fragment thereof of a human heavy chain; said CDR1 having the amino acid sequence SEQ ID NO:1, said CDR2 having the amino acid sequence SEQ ID NO:2, and said CDR3 having the amino acid sequence SEQ ID NO:3; and

b) an immunoglobulin light chain or fragment thereof which comprises a variable domain comprising in sequence the hypervariable regions and optionally also the CDR1', CDR2', and CDR3' hypervariable regions or direct CDR' equivalents thereof and the constant part or fragment thereof of a human light chain, said CDR1' having the amino acid sequence SEQ ID NO: 4, said CDR2' having the amino acid sequence SEQ ID NO:5, and said CDR3' having the amino acid sequence SEQ ID NO:6.

In one embodiment, an IL-17 binding molecule (e.g., IL-17 antibody, e.g., AIN457) is selected from a single chain binding molecule which comprises an antigen binding site comprising:

a) a first domain comprising in sequence the hypervariable regions CDR1, CDR2 and CDR3 or direct CDR equivalents thereof, said CDR1 having the amino acid sequence SEQ ID NO:1, said CDR2 having the amino acid sequence SEQ ID NO:2, and said CDR3 having the amino acid sequence SEQ ID NO: 3; and

b) a second domain comprising the hypervariable regions CDR1', CDR2' and CDR3' or direct CDR' equivalents thereof, said CDR1' having the amino acid sequence SEQ ID NO:4, said CDR2' having the amino acid sequence SEQ ID NO:5, and said CDR3' having the amino acid sequence SEQ ID NO:6; and

c) a peptide linker which is bound either to the N-terminal extremity of the first domain and to the C-terminal extremity of the second domain or to the C-terminal extremity of the first domain and to the N-terminal extremity of the second domain.

By the term "direct CDR equivalents thereof" are meant IL-17 binding molecules comprising in sequence the hypervariable regions CDR1_i, CDR2_i, and CDR3_i, (instead of CDR1, CDR2, and CDR3), wherein

- (i) the hypervariable region CDR1_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region CDR1 as shown in SEQ ID NO: 1; and
- (ii) the hypervariable region CDR2_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region CDR2 as shown in SEQ ID NO: 2; and
- (iii) the hypervariable region CDR3_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region CDR3 as shown in SEQ ID NO: 3; and
- (iv) such a molecule comprising in sequence the hypervariable regions CDR1_i, CDR2_i, and CDR3_i is capable of inhibiting the activity of 1 nM (= 30ng/ml) human IL-17 at a concentration of 50 nM, preferably 20nM, more preferably 10 nM, more preferably 5 nM of said molecule by 50%, said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Similarly, by the term "direct CDR-x equivalents thereof" are meant IL-17 binding molecules comprising in sequence the hypervariable regions CDR1_{i-x}, CDR2_{i-x}, and CDR3_{i-x}, (instead of CDR1-x, CDR2-x, and CDR3-x), wherein

- (i) the hypervariable region CDR1_{i-x} differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region CDR1-x as shown in SEQ ID NO: 11; and
- (ii) the hypervariable region CDR2_{i-x} differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region CDR2-x as shown in SEQ ID NO: 12; and

- (iii) the hypervariable region CDR3_{i-x} differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region CDR3-x as shown in SEQ ID NO: 13; and
- (iv) such a molecule comprising in sequence the hypervariable regions CDR1_{i-x}, CDR2_{i-x}, and CDR3_{i-x} is capable of inhibiting the activity of 1 nM (= 30ng/ml) human IL-17 at a concentration of 50 nM, preferably 20nM, more preferably 10 nM, more preferably 5 nM of said molecule by 50%, said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Similarly, by the term "direct CDR' equivalents thereof" is meant a domain comprising in sequence the hypervariable regions CDR1'_i, CDR2'_i, and CDR3'_i, wherein

- (i) the hypervariable region CDR1'_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region CDR1' as shown in SEQ ID NO: 4; and
- (ii) the hypervariable region CDR2'_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region CDR2' as shown in SEQ ID NO: 5; and
- (iii) the hypervariable region CDR3'_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region CDR3' as shown in SEQ ID NO: 6; and
- (iv) such a molecule comprising in sequence the hypervariable regions CDR1'_i, CDR2'_i, and CDR3'_i is capable of inhibiting the activity of 1 nM (= 30ng/ml) human IL-17 at a concentration of 50 nM, preferably 20nM, more preferably 10 nM, more preferably 5 nM of said molecule by 50%, said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Alternatively, an IL-17 binding molecule (e.g., IL-17 antibody, e.g., AIN457) may comprise at least one antigen binding site comprising at least one immunoglobulin heavy chain variable domain (V_H) which comprises in sequence:

- a) hypervariable regions CDR1 (SEQ ID NO: 1), CDR2 (SEQ ID NO: 2) and CDR3 (SEQ ID NO: 3); or

b) hypervariable regions CDR1_i, CDR2_i, CDR3_i, said hypervariable region CDR1_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR1 as shown in SEQ ID NO: 1, said hypervariable region CDR2_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR2 as shown in SEQ ID NO: 2; and said hypervariable region CDR3_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR3 as shown in SEQ ID NO: 3; and said binding IL-17 molecule comprising in sequence the hypervariable regions CDR1_x, CDR2_x, and CDR3_x is capable of inhibiting the activity of about 1 nM (= 30ng/ml) human IL-17 at a concentration of about 50 nM or less, about 20 nM or less, about 10 nM or less, about 5 nM or less, about 2 nM or less, or more preferably of about 1 nM or less of said molecule by 50%, said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Similarly, an IL-17 binding molecule (e.g., IL-17 antibody, e.g., AIN457) may comprise at least one antigen binding site comprising at least one immunoglobulin heavy chain variable domain (V_H) which comprises in sequence

a) hypervariable regions CDR1-x (SEQ ID NO: 11), CDR2-x (SEQ ID NO: 12) and CDR3-x (SEQ ID NO: 13); or

b) hypervariable regions CDR1_{i-x}, CDR2_{i-x}, CDR3_{i-x}, said hypervariable region CDR1_{i-x} differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR1-x as shown in SEQ ID NO: 11, said hypervariable region CDR2_{i-x} differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR2-x as shown in SEQ ID NO: 12; and said hypervariable region CDR3_{i-x} differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR3-x as shown in SEQ ID NO: 13; and said binding IL-17 molecule comprising in sequence the hypervariable regions CDR1_{i-x}, CDR2_{i-x}, and CDR3_{i-x} is capable of inhibiting the activity of 1 nM (= 30ng/ml) human IL-17 at a concentration of about 50 nM or less, about 20 nM or less, about 10 nM or less, about 5 nM or less, about 2 nM or less, or more preferably of about 1 nM or less of said molecule by 50%, said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Similarly, an IL-17 binding molecule (e.g., IL-17 antibody, e.g., AIN457) may comprise at least one antigen binding site comprising at least one immunoglobulin light chain variable domain (V_L) which comprises in sequence

a) hypervariable regions CDR'1 (SEQ ID NO: 4), CDR'2 (SEQ ID NO: 5) and CDR'3 (SEQ ID NO: 6); or

b) hypervariable regions CDR1'_i, CDR2'_i, CDR3'_i, said hypervariable region CDR'1_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR'1 as shown in SEQ ID NO: 4, said hypervariable region CDR'2_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR'2 as shown in SEQ ID NO: 5; and said hypervariable region CDR'3_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR'3 as shown in SEQ ID NO: 6; and said binding IL-17 molecule comprises in sequence the hypervariable regions CDR'1_i, CDR'2_i, and CDR'3_i is capable of inhibiting the activity of 1 nM (= 30ng/ml) human IL-17 at a concentration of about 50 nM or less, about 20 nM or less, about 10 nM or less, about 5 nM or less, about 2 nM or less, or more preferably of about 1 nM or less of said molecule by 50%, said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Alternatively, an IL-17 binding molecule (e.g., IL-17 antibody, e.g., AIN457) may comprise both heavy (V_H) and light chain (V_L) variable domains and said IL-17 binding molecule comprises at least one antigen binding site comprising:

a) an immunoglobulin heavy chain variable domain (V_H) which comprises in sequence hypervariable regions CDR1 (SEQ ID NO: 1), CDR2 (SEQ ID NO: 2) and CDR3 (SEQ ID NO: 3); and an immunoglobulin light chain variable domain (V_L) which comprises in sequence hypervariable regions CDR1' (SEQ ID NO: 4), CDR2' (SEQ ID NO: 5) and CDR3' (SEQ ID NO: 6); or

b) an immunoglobulin heavy chain variable domain (V_H) which comprises in sequence hypervariable regions CDR1_i, CDR2_i, and CDR3_i, said hypervariable region hypervariable regions CDR1_i, CDR2_i, CDR3_i, said hypervariable region CDR1_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR1 as shown in SEQ ID NO: 1, said hypervariable region CDR2_i differs by 3, preferably 2,

more preferably 1 amino acid(s) from the hypervariable region of CDR2 as shown in SEQ ID NO: 2; and said hypervariable region CDR3_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR3 as shown in SEQ ID NO: 3; and an immunoglobulin light chain variable domain (V_L) which comprises in sequence hypervariable regions CDR1'_i, CDR2'_i, CDR3'_i, said hypervariable region CDR'1_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR'1 as shown in SEQ ID NO: 4, said hypervariable region CDR'2_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR'2 as shown in SEQ ID NO: 5; and said hypervariable region CDR'3_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR'3 as shown in SEQ ID NO: 6; and said binding IL-17 molecule defined in b) comprises in sequence the hypervariable regions CDR1_i, CDR2_i, CDR3_i, CDR'1_i, CDR'2_i, and CDR'3_i is capable of inhibiting the activity of 1 nM (= 30ng/ml) human IL-17 at a concentration of about 50 nM or less, about 20 nM or less, about 10 nM or less, about 5 nM or less, about 2 nM or less, or more preferably of about 1 nM or less of said molecule by 50%, said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Alternatively, an IL-17 binding molecule (e.g., IL-17 antibody, e.g., AIN457) may comprise both heavy (V_H) and light chain (V_L) variable domains and said IL-17 binding molecule comprises at least one antigen binding site comprising:

a) an immunoglobulin heavy chain variable domain (V_H) which comprises in sequence hypervariable regions CDR1-x (SEQ ID NO:11), CDR2-x (SEQ ID NO:12) and CDR3-x (SEQ ID NO:13); and an immunoglobulin light chain variable domain (V_L) which comprises in sequence hypervariable regions CDR1' (SEQ ID NO: 4), CDR2' (SEQ ID NO: 5) and CDR3' (SEQ ID NO:6); or

b) an immunoglobulin heavy chain variable domain (V_H) which comprises in sequence hypervariable regions CDR1_i-x, CDR2_i-x, and CDR3_i-x, said hypervariable region hypervariable regions CDR1_i-x, CDR2_i-x, CDR3_i-x, said hypervariable region CDR1_i-x differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR1-x as shown in SEQ ID NO: 11, said hypervariable region CDR2_i-x differs by 3, preferably 2, more preferably 1 amino acid(s) from the

hypervariable region of CDR2-x as shown in SEQ ID NO: 12; and said hypervariable region CDR3_i-x differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR3-x as shown in SEQ ID NO: 13; and an immunoglobulin light chain variable domain (V_L) which comprises in sequence hypervariable regions CDR1'_i, CDR2'_i, CDR3'_i, said hypervariable region CDR'1_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR'1 as shown in SEQ ID NO: 4, said hypervariable region CDR'2_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR'2 as shown in SEQ ID NO:5; and said hypervariable region CDR'3_i differs by 3, preferably 2, more preferably 1 amino acid(s) from the hypervariable region of CDR'3 as shown in SEQ ID NO: 6; and said binding IL-17 molecule defined in b) comprises in sequence the hypervariable regions CDR1_i, CDR2_i, CDR3_i, CDR'1_i, CDR'2_i, and CDR'3_i is capable of inhibiting the activity of 1 nM (= 30ng/ml) human IL-17 at a concentration of about 50 nM or less, about 20 nM or less, about 10 nM or less, about 5 nM or less, about 2 nM or less, or more preferably of about 1 nM or less of said molecule by 50%, said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

A human IL-17 antibody disclosed herein may comprise a heavy chain that is substantially identical to that set forth as SEQ ID NO:17 and a light chain that is substantially identical to that set forth as SEQ ID NO:15. A human IL-17 antibody disclosed herein may comprise a heavy chain that comprises SEQ ID NO:17 and a light chain that comprises SEQ ID NO:15.

A human IL-17 antibody disclosed herein may comprise:

a) one heavy chain which comprises a variable domain having an amino acid sequence substantially identical to that shown in SEQ ID NO:8 starting with the amino acid at position 1 and ending with the amino acid at position 127 and the constant part of a human heavy chain; and

b) one light chain which comprises a variable domain having an amino acid sequence substantially identical to that shown in SEQ ID NO:10 starting with the amino acid at position 1 and ending with the amino acid at position 109 and the constant part of a human light chain.

The inhibition of the binding of IL-17 to its receptor may be conveniently tested in various assays including such assays as described in WO 2006/013107. By the term "to the same extent" is meant that the reference and the equivalent molecules exhibit, on a statistical basis, essentially identical IL-17 inhibitory activity in one of the assays referred to herein (see Example 1 of WO 2006/013107). For example, IL-17 binding molecules of the disclosure typically have IC_{50} s for the inhibition of human IL-17 on IL-6 production induced by human IL-17 in human dermal fibroblasts which are below about 10 nM, more preferably about 9, 8, 7, 6, 5, 4, 3, 2, or about 1 nM of that of, preferably substantially the same as, the IC_{50} of the corresponding reference molecule when assayed as described in Example 1 of WO 2006/013107.

Alternatively, the assay used may be an assay of competitive inhibition of binding of IL-17 by soluble IL-17 receptors (e.g. the human IL-17 R/Fc constructs of Example 1 of WO 2006/013107) and the IL-17 binding molecules of the disclosure.

The disclosure provides methods for treating PMR (either isolated or associated with GCA), comprising administering a therapeutically effective amount of an IL-17 binding molecules, e.g., IL-17 antibodies, such as AIN457, to a subject suffering from PMR, wherein said IL-17 binding molecule is encoded by a DNA as described herein.

An IL-17 binding molecule of the disclosure may be produced by recombinant DNA techniques. In view of this, one or more DNA molecules encoding the binding molecule must be constructed, placed under appropriate control sequences and transferred into a suitable host organism for expression.

In a very general manner, there are accordingly provided

- (i) DNA molecules encoding a single domain IL-17 binding molecule of the disclosure, a single chain IL-17 binding molecule of the disclosure, an IL-17 binding molecule comprising a heavy and light chain as defined herein, or fragments of a IL-17 binding molecule of the disclosure; and
- (ii) the use of the DNA molecules of the disclosure for the production of a IL-17 binding molecule of the disclosure by recombinant means.

The disclosure provides a DNA construct comprising a DNA molecule which is substantially identical to SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:14, or SEQ ID NO:15.

Furthermore, the disclosure provides a DNA construct comprising two DNA molecules of which one is substantially identical to SEQ ID NO:7 or is a direct DNA_H equivalent thereof and the other substantially identical to SEQ ID NO:9, or is a direct DNA_L equivalent thereof.

Furthermore, the disclosure provides a DNA construct comprising two DNA molecules of which one is substantially identical to SEQ ID NO:14 (AIN457 light chain DNA) or is a direct DNA_H equivalent thereof and the other substantially identical to SEQ ID NO:16 (AIN457 heavy chain DNA), or is a direct DNA_L equivalent thereof.

The present state of the art is such that the skilled worker in the art is able to synthesize the DNA molecules of the disclosure given the information provided herein i.e. the amino acid sequences of the hypervariable regions and the DNA sequences coding for them. A method for constructing a variable domain gene is for example described in EPA 239 400 and may be briefly summarized as follows: a gene encoding a variable domain of a MAb of whatever specificity is cloned. The DNA segments encoding the framework and hypervariable regions are determined and the DNA segments encoding the hypervariable regions are removed so that the DNA segments encoding the framework regions are fused together with suitable restriction sites at the junctions. The restriction sites may be generated at the appropriate positions by mutagenesis of the DNA molecule by standard procedures. Double stranded synthetic CDR cassettes are prepared by DNA synthesis according to the sequences encoding for SEQ ID NO:1 (CDR1), SEQ ID NO:2 (CDR2), SEQ ID NO:3 (CDR3), SEQ ID NO:4 (CDR1'), SEQ ID NO:5 (CDR2'), SEQ ID NO:6 (CDR6'), SEQ ID NO:11 (CDR1-x), SEQ ID NO:12 (CDR2-x), SEQ ID NO:13 (CDR3-x),. These cassettes are provided with sticky ends so that they can be ligated at the junctions of the framework

Furthermore, it is not necessary to have access to the mRNA from a producing hybridoma cell line in order to obtain a DNA construct coding for the IL-17 binding molecules of the disclosure. Thus PCT application WO 90/07861 gives full instructions for the production of an antibody by recombinant DNA techniques given only written information as to the nucleotide sequence of the gene. The method comprises the synthesis of a number of oligonucleotides, their amplification by the PCR method, and their splicing to give the desired DNA sequence.

Expression vectors comprising a suitable promoter or genes encoding heavy and light chain constant parts are publicly available. Thus, once a DNA molecule of the disclosure is prepared it may be conveniently transferred in an appropriate expression vector. DNA molecules encoding single chain antibodies may also be prepared by standard methods, for example, as described in WO 88/1649.

In analogy to the case for CDR equivalents, the term "direct DNA_H equivalents thereof" is meant to stand for a first DNA construct encoding a heavy chain or fragment thereof of an IL-17 binding molecule of the disclosure and comprises:

a) a first part which encodes a variable domain comprising alternatively framework and hypervariable regions, said hypervariable regions being in sequence CDR1_i, CDR2_i and CDR3_i, said CDR1_i is at least 50% identical, preferably at least 60, 70, 80, 85, or 90% identical, more preferably at least 95% identical to the hypervariable region CDR1 as shown in SEQ ID NO: 1, said CDR2_i is at least 50% identical, preferably at least 60, 70, 80, 85, or 90% identical, more preferably at least 95% identical to the hypervariable region CDR2 as shown in SEQ ID NO:2, and CDR3_i is at least 50% identical, preferably at least 60, 70, 80, 85, or 90% identical, more preferably at least 95% identical to the hypervariable region CDR3 as shown in SEQ ID NO: 3; this first part starting with a codon encoding the first amino acid of the variable domain and ending with a codon encoding the last amino acid of the variable domain; and

b) a second part encoding a heavy chain constant part or fragment thereof which starts with a codon encoding the first amino acid of the constant part of the heavy chain and ends with a codon encoding the last amino acid of the constant part or fragment thereof, followed by a stop codon; and

c) said DNA construct encoding for a polypeptide which is capable either alone or in combination with another polypeptide of inhibiting the activity of 1 nM (= 30ng/ml) human IL-17 at a concentration of 50 nM, preferably 20nM, more preferably 10 nM, more preferably 5 nM of said molecule by 50%, said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Similarly, the term "direct DNA_{H-x} equivalents thereof" is meant to stand for a first alternative DNA construct encoding a heavy chain or fragment thereof of an IL-17 binding molecule (e.g., IL-17 antibody, e.g., AIN457) and comprises:

a) a first part which encodes a variable domain comprising alternatively framework and hypervariable regions, said hypervariable regions being in sequence CDR1_{i-x}, CDR2_{i-x} and CDR3_{i-x}, said CDR1_{i-x} is at least 50% identical, preferably at least 60, 70, 80, 85, or 90% identical, more preferably at least 95% identical to the hypervariable region CDR1 as shown in SEQ ID NO:11, said CDR2_{i-x} is at least 50% identical, preferably at least 60, 70, 80, 85, or 90% identical, more preferably at least 95% identical to the hypervariable region CDR2 as shown in SEQ ID NO:12, and CDR3_{i-x} is at least 50% identical, preferably at least 60, 70, 80, 85, or 90% identical, more preferably at least 95% identical to the hypervariable region CDR3 as shown in SEQ ID NO:13; this first part starting with a codon encoding the first amino acid of the variable domain and ending with a codon encoding the last amino acid of the variable domain; and

b) a second part encoding a heavy chain constant part or fragment thereof which starts with a codon encoding the first amino acid of the constant part of the heavy chain and ends with a codon encoding the last amino acid of the constant part or fragment thereof, followed by a stop codon; and

c) said DNA construct encoding for a polypeptide which is capable either alone or in combination with another polypeptide of inhibiting the activity of 1 nM (= 30ng/ml) human IL-17 at a concentration of about 50 nM or less, about 20 nM or less, about 10 nM or less, about 5 nM or less, about 2 nM or less, or more preferably of about 1 nM or less of said molecule by 50%, said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Preferably, these DNA constructs encode a variable domain comprising alternatively framework and hypervariable regions, said hypervariable regions being in sequence CDR1, CDR2 and CDR3, said CDR1 having the amino acid sequence SEQ ID NO:1, said CDR2 having the amino acid sequence SEQ ID NO:2, and said CDR3 having the amino acid sequence SEQ ID NO: 3. More preferably, these DNA constructs encode a variable domain comprising alternatively framework and hypervariable regions, said hypervariable regions being in sequence CDR1-x, CDR2-x and CDR3-x, said CDR1-x having the amino acid sequence SEQ ID NO:11, said CDR2-x having the amino acid sequence SEQ ID NO:12, and said CDR3-x having the amino acid sequence SEQ ID NO:

13. More preferably, this first part encodes a variable domain having an amino acid sequence substantially identical to the amino acid sequence as shown in SEQ ID NO:8 starting with the amino acid at position 1 and ending with the amino acid at position 127. More preferably the first part has the nucleotide sequence as shown in SEQ ID NO: 7 starting with the nucleotide at position 1 and ending with the nucleotide at position 381. Also preferably, the second part encodes the constant part of a human heavy chain, more preferably the constant part of the human γ 1 chain. This second part may be a DNA fragment of genomic origin (comprising introns) or a cDNA fragment (without introns).

Similarly, the term "direct DNA_L equivalents thereof" is meant to stand for a second DNA construct encoding a light chain or fragment thereof of an IL-17 binding molecule (e.g., IL-17 antibody, e.g., AIN457) of the disclosure and comprises:

a) a first part which encodes a variable domain comprising alternatively framework and hypervariable regions; said hypervariable regions being CDR3_i' and optionally CDR1_i' and CDR2_i', said CDR1_i' is at least 50% identical, preferably at least 60, 70, 80, 85, or 90% identical, more preferably at least 95% identical to the hypervariable region CDR1' as shown in SEQ ID NO: 4, said CDR2_i' is at least 50% identical, preferably at least 60, 70, 80, 85, or 90% identical, more preferably at least 95% identical to the hypervariable region CDR2' as shown in SEQ ID NO: 5, and said CDR3_i' is at least 50% identical, preferably at least 60, 70, 80, 85, or 90% identical, more preferably at least 95% identical to the hypervariable region CDR3' as shown in SEQ ID NO: 6; this first part starting with a codon encoding the first amino acid of the variable domain and ending with a codon encoding the last amino acid of the variable domain; and

b) a second part encoding a light chain constant part or fragment thereof which starts with a codon encoding the first amino acid of the constant part of the light chain and ends with a codon encoding the last amino acid of the constant part or fragment thereof followed by a stop codon; and

c) said DNA construct encoding for a polypeptide which is capable either alone or in combination with another polypeptide of inhibiting the activity of 1 nM (= 30ng/ml) human IL-17 at a concentration of 50 nM, preferably 20nM, more preferably 10 nM, more preferably 5 nM of said molecule by 50%, said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Preferably, this second DNA construct encodes a variable domain comprising alternatively framework and hypervariable regions, said hypervariable regions being in sequence CDR1', CDR2' and CDR3', said CDR1' having the amino acid sequence SEQ ID NO:4, said CDR2' having the amino acid sequence SEQ ID NO:5, and said CDR3' having the amino acid sequence SEQ ID NO:6. More preferably, this first part of the second DNA construct encodes a variable domain having an amino acid sequence substantially identical to the amino acid sequence as shown in SEQ ID NO:10 starting with the amino acid at position 1 and ending with the amino acid at position 109. More preferably, the first part has the nucleotide sequence as shown in SEQ ID NO:9 starting with the nucleotide at position 1 and ending with the nucleotide at position 327. Also preferably the second part encodes the constant part of a human light chain, more preferably the constant part of the human κ

Preferably, the first and second DNA construct will be used together, but may be also used separately.

The disclosure also includes IL-17 binding molecules in which one or more of the amino acid residues of CDR1, CDR2, CDR3, CDR1-x, CDR2-x, CDR3-x, CDR1', CDR2' or CDR3' or the frameworks, typically only a few (e.g., 1-4), are changed; for instance by mutation, e.g., site directed mutagenesis of the corresponding DNA sequences. The disclosure includes the DNA sequences coding for such changed IL-17 binding molecules. In particular the disclosure includes IL-17 binding molecules in which one or more residues of CDR1' or CDR2' have been changed from the residues shown in SEQ ID NO:4 (for CDR1') and SEQ ID NO:5 (for CDR2').

In the first and second DNA constructs, the first and second parts may be separated by an intron, and, an enhancer may be conveniently located in the intron between the first and second parts. The presence of such an enhancer which is transcribed but not translated, may assist in efficient transcription. In particular embodiments the first and second DNA constructs comprise the enhancer of a heavy chain gene advantageously of human origin.

Each of the DNA constructs are placed under the control of suitable control sequences, in particular under the control of a suitable promoter. Any kind of promoter

may be used, provided that it is adapted to the host organism in which the DNA constructs will be transferred for expression.

The desired antibody may be produced in a cell culture or in a transgenic animal. A suitable transgenic animal may be obtained according to standard methods which include micro injecting into eggs the first and second DNA constructs placed under suitable control sequences transferring the so prepared eggs into appropriate pseudo-pregnant females and selecting a descendant expressing the desired antibody.

When the antibody chains are produced in a cell culture, the DNA constructs must first be inserted into either a single expression vector or into two separate but compatible expression vectors, the latter possibility being preferred.

IL-17 binding molecules as defined above which have binding specificity for human IL-17, in particular antibodies which are capable of inhibiting the binding of IL-17 to its receptor; and antibodies to IL-17 which are capable of inhibiting the activity of 1 nM (= 30 ng/ml) human IL-17 at a concentration of about 50 nM or less, about 20 nM or less, about 10 nM or less, about 5 nM or less, about 2 nM or less, or more preferably of about 1 nM or less of said molecule by 50%, said inhibitory activity is measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts, are herein referred to as Antibodies of the Disclosure.

The IL-17 binding molecules block the effects of IL-17 on its target cells and thus are indicated for use in the treatment of IL-17 mediated diseases and disorders. The disclosed IL-17 binding molecules are useful for the prophylaxis and treatment of IL-17 mediated diseases or medical conditions, e.g., inflammatory conditions, allergies and allergic conditions, hypersensitivity reactions, autoimmune diseases, severe infections, and organ or tissue transplant rejection.

The disclosed IL-17 binding molecules may be used for the treatment of recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants, including allograft rejection or xenograft rejection, and for the prevention of graft-versus-host disease, such as following bone marrow transplant, and organ transplant associated arteriosclerosis.

Treatment Regimens

The disclosed IL-17 binding molecules, e.g., an IL-17 antibody, such as AIN457, are useful for the treatment, prevention, or amelioration of vasculitis, e.g., inflammatory large vessel vasculitis (e.g., GCA [i.e., isolated GCA and GCA associated with PMR]), and PMR [i.e., isolated PMR and PMR associated with GCA]). Examples of vasculitis include, e.g., Behcet's Disease, Buerger's disease (thromboangiitis obliterans), Churg-Strauss syndrome (allergic granulomatosis and allergic angiitis), cryoglobulinemia, giant cell arteritis (GCA), Henoch-Schonlein purpura, hypersensitivity vasculitis, Kawasaki disease (mucocutaneous lymph node syndrome), microscopic polyangiitis (PA), polyarteritis nodosa, rheumatoid vasculitis, Takayasu's arteritis, Wegener's granulomatosis, and polymyalgia rheumatica (PMR), Blau's syndrome, primary systemic vasculitis, essential cryoglobulinemic vasculitis, and urticarial vasculitis.

The IL-17 binding molecules, e.g., an IL-17 antibody, such as AIN457, may be used *in vitro*, *ex vivo*, or incorporated into pharmaceutical compositions and administered to individuals (e.g., human subjects) *in vivo* to treat, ameliorate, or prevent, e.g., PMR (either isolated PMR or PMR associated with GCA) and GCA (either isolated GCA or GCA associated with PMR). A pharmaceutical composition will be formulated to be compatible with its intended route of administration (e.g., oral compositions generally include an inert diluent or an edible carrier). Other nonlimiting examples of routes of administration include parenteral (e.g., intravenous), intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration. The pharmaceutical compositions compatible with each intended route are well known in the art.

The IL-17 binding molecules, e.g., an IL-17 antibody, such as AIN457, may be used as a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may contain, in addition to an IL-17 binding molecule, carriers, various diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The characteristics of the carrier will depend on the route of administration.

The pharmaceutical compositions for use in the disclosed methods may also contain additional therapeutic agents for treatment of the particular targeted disorder. For example, a pharmaceutical composition may also include anti-inflammatory agents. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with the IL-17 binding molecules, or to minimize side effects caused by the IL-17 binding molecules.

The pharmaceutical composition of the disclosure may be in the form of a liposome in which the IL-17 binding molecule is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids that exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, etc.

In practicing the method of treatment or use of the present disclosure, a therapeutically effective amount of an IL-17 binding molecule is administered to a subject, e.g., a mammal (e.g., a human). An IL-17 binding molecule may be administered in accordance with the method of the disclosure either alone or in combination with other therapies, such as, e.g., in combination with additional therapies for inflammation, e.g., Illaris® (canakinumab, ACZ885). When coadministered with one or more agents, an IL-17 binding molecule may be administered either simultaneously with the other agent, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering the IL-17 binding molecule in combination with other agents.

When a therapeutically effective amount of an IL-17 binding molecule is administered orally, the binding agent will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the disclosure may additionally contain a solid carrier such as a gelatin or an adjuvant. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil (exercising caution in relation to peanut allergies), mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline

solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol.

When a therapeutically effective amount of an IL-17 binding molecule is administered by intravenous, cutaneous or subcutaneous injection, the IL-17 binding molecule will be in the form of a pyrogen-free, parenterally acceptable solution. A pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection may contain, in addition to the IL-17 binding molecule, an isotonic vehicle such as sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer's injection, or other vehicle as known in the art.

Pharmaceutical compositions for use in the disclosed methods may be manufactured in conventional manner. In one embodiment, the pharmaceutical composition is preferably provided in lyophilized form. For immediate administration it is dissolved in a suitable aqueous carrier, for example sterile water for injection or sterile buffered physiological saline. If it is considered desirable to make up a solution of larger volume for administration by infusion rather than a bolus injection, it is advantageous to incorporate human serum albumin or the patient's own heparinised blood into the saline at the time of formulation. The presence of an excess of such physiologically inert protein prevents loss of antibody by adsorption onto the walls of the container and tubing used with the infusion solution. If albumin is used, a suitable concentration is from 0.5 to 4.5% by weight of the saline solution. Other formulations comprise liquid or lyophilized formulation.

The appropriate dosage will, of course, vary depending upon, for example, the particular IL-17 binding molecule to be employed, the host, the mode of administration and the nature and severity of the condition being treated, and on the nature of prior treatments that the patient has undergone. Ultimately, the attending physician will decide the amount of the IL-17 binding molecule with which to treat each individual subject. In some embodiments, the attending physician may administer low doses of the IL-17 binding molecule and observe the subject's response. In other embodiments, the initial dose(s) of IL-17 binding molecule administered to a subject are high, and then are titrated downward until signs of relapse occur. Larger doses of the IL-17 binding molecule may

be administered until the optimal therapeutic effect is obtained for the subject, and at that point the dosage is not generally increased further.

An IL-17 binding molecule is conveniently administered parenterally, intravenously, e.g. into the antecubital or other peripheral vein, intramuscularly, or subcutaneously.

In prophylactic use, satisfactory results are generally indicated to be obtained at dosages from about 0.05 mg to about 10 mg per kilogram body weight, more, usually from about 0.1 mg to about 10 mg per kilogram body weight. The frequency of dosing for prophylactic uses will normally be in the range from about once per week up to about once every three months, more usually in the range from about once every 2 weeks up to about once every 10 weeks, e.g., once every four to eight weeks. A prophylactic treatment typically comprises administering the IL-17 binding molecule once per month to once every two to three months, or less frequently.

In some embodiments, the IL-17 binding molecules are administered as a single dose infusion (e.g., a single dose infusion of about 1 mg/kg, about 3 mg/kg, about 5 mg/kg, about 10 mg/kg, or about 20 mg/kg) or as multi-dose infusions, e.g., two, three, four, five, or more doses of about 1 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 10 mg/kg or about 20 mg/kg are administered two, three, four, five, or more weeks apart. In another embodiment, an IL-17 binding molecule is administered s.c. weekly, every other week, or monthly at a dosage of about 25 mg, about 75 mg, about 150 mg, about 300 mg or about 500 mg. In one embodiment, the IL-17 binding molecule is administered at about 300 mg s.c. weekly for three weeks, about 300 mg s.c. at baseline and week two, or about 150 mg s.c. at baseline and week two. In other embodiments, the IL-17 binding molecule is administered at about 150 mg s.c. every four weeks, or about 300 mg s.c. every two weeks, or about 300 mg s.c. every four weeks (monthly). In other embodiments, the IL-17 binding molecule is administered at about 300 mg s.c. at baseline (day zero), week one and week two then every two weeks; 300 mg s.c. at baseline (day zero) and week two, then every four weeks (monthly); or about 150 mg s.c. at baseline (day zero) and week two, then every four weeks.

In one embodiment, the IL-17 binding molecule is administered as a single dose intravenous infusion of about 1 to about 10 mg/kg, or as a subcutaneous injection of up to

about 300 mg. The infusion or subcutaneous injection can be repeated as frequently as once or twice per week, or as infrequently as every six months, depending on the response of symptoms, signs, and laboratory tests such as the sedimentation rate.

In another embodiment, the IL-17 binding molecule is administered subcutaneously as a about 25 mg, about 75 mg, about 150 mg, about 300 mg dose fixed daily, weekly, or monthly.

In another embodiment, the IL-17 binding molecule is administered intravenously up to about 10 mg/kg weekly to monthly.

In another embodiment, the IL-17 binding molecule is administered as a single dose intravenous infusion of 3 mg/kg.

The duration of intravenous (i.v.) therapy using a pharmaceutical composition of the present disclosure will vary, depending on the severity of the disease being treated and the condition and personal response of each individual patient. Also contemplated is subcutaneous (s.c.) therapy using a pharmaceutical composition of the present disclosure. The attending physician will decide on the appropriate duration of i.v. or s.c. therapy, or therapy with a small molecule, and the timing of administration of the therapy, using the pharmaceutical composition of the present disclosure.

The IL-17 binding molecules of the present disclosure are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified herein. Uses or activities described for the IL-17 binding molecules may be provided by administration or use of such IL-17 binding molecules or by administration or use of polynucleotides encoding such IL-17 binding molecules (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

The disclosed IL-17 binding molecules, e.g., an IL-17 antibody, such as AIN457, are additionally useful for the treatment, prevention, or amelioration of IL-17 mediated diseases and disorders, e.g., diseases associated with increased or aberrant IL-17 signal. Such disorders may include, e.g., Periodic Fever Syndromes: Familial Mediterranean Fever (FMF), Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D syndrome (HIDS), also called Mevalonate Kinase Associated Periodic Fever Syndrome, Familial Cold auto inflammatory syndrome and Periodic fever, Aphthous-stomatitis, Pharyngitis, Adenitis (PFAPA) Syndrome, anti-synthetase

syndrome, Macrophage activation syndrome MAS, Behçet Disease, Blau's syndrome, PAPA syndrome, Schnitzler's syndrome, Sweet's syndrome, Henoch-Schoenlein purpura, primary systemic vasculitis, Kawasaki disease (mucocutaneous lymph node syndrome), Takayasu arteritis, Polyarteritis nodosa, Essential cryoglobulinemic vasculitis, microscopic polyangiitis (MPA) and Churg–Strauss syndrome (CSS), urticarial vasculitis, sarcoidosis, pemphigus, rheumatic fever, fibromyalgia, ankylosing spondylitis, Alzheimer disease, amyloidosis, secondary amyloidosis and adult onset Still disease (AOSD), HLA-B27 associated diseases, such as psoriatica, spondylitis ankylosans, Morbus Reiter and enteropathic arthritis, Juvenile rheumatoid arthritis, adult rheumatoid arthritis, Muckle Wells Syndrome, transplantation and tissue/cell/skin grafting, multiple myeloma, multiple sclerosis, Lupus erythematosus, Type 1 diabetes, Type II diabetes, sarcoidosis, scleritis, cardiovascular disease, histiocytosis, dry eye, fungal infections (e.g., invasive infections caused by aspergillosis and candida), bacterial infections, viral infections, e.g., hematogenic osteomyelitis, infectious arthritis, tuberculous arthritis.

Additional disorders treatable by the disclosed IL-17 binding molecules include tuberculosis, Hansen's disease (leprosy), histoplasmosis, aspergillosis, blastomycosis, coccidiomycosis, cryptococcosis, cat-scratch disease (i.e., Bartonella infection), Pneumocystic pneumonia, Whipple's disease, Crohn's disease, Histiocytosis X (comprising Langerhans cell histiocytosis, juvenile xanthogranuloma, hemophagocytic lymphohistiocytosis, Niemann-Pick disease, sea-blue histiocyte syndrome, acute monocytic leukemia, malignant histiocytosis, and Erdheim-Chester disease), Chronic granulomatous disease (e.g., NADPH oxidase deficiency), Granulomatous drug reactions, brain injury, ischemia and reperfusion, Celiac disease (CD), obesity, necrosis (either separately or accompanying septic shock), Cystic Fibrosis, Urogenital Diseases and neoplasms, Pre-eclampsia, Hepatitis B/C, Parasitic diseases, Chronic obstructive pulmonary disease (COPD), Acrodermatitis hallopeau, Histiocytosis X, and Ozone mediated neutrophilia

Accordingly, provided herein is a method of treating vasculitis in a subject comprising, administering a therapeutically effective amount of an IL-17 binding molecule to a subject in need thereof, wherein said IL-17 binding molecule comprises

- a) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- b) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- c) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- d) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- e) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- f) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- g) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or
- h) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6.

Further provided herein is an IL-17 binding molecule for use in the treatment of vasculitis, wherein said IL-17 binding molecule comprises

- a) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- b) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- c) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;

- d) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- e) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- f) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- g) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or
- h) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6.

Further provided herein is the use of an IL-17 binding molecule for the preparation of a medicament for the treatment of vasculitis, wherein said IL-17 binding molecule comprises

- a) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- b) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- c) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- d) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- e) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- f) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;

- g) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or
- h) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6.

In some embodiments of the disclosed methods, IL-17 binding molecules or uses the IL-17 binding molecule is AIN457 (secukinumab). In further embodiments, the vasculitis is an autoimmune vasculitis or a large vessel vasculitis. In further embodiments, the vasculitis is isolated PMR. In further embodiments, the vasculitis is PMR associated with GCA. In further embodiments, the vasculitis is isolated GCA. In further embodiments, the vasculitis is GCA associated with PMR. In one embodiment, an additional agent for use in the disclosed methods or uses, or to be co-administered with a disclosed IL-17 binding molecule, is selected from the group consisting of prednisone, methotrexate, prednisolone, methylprednisone, methylprednisolone and deflazacort.

Disclosed herein is also a method of treating vasculitis in a subject in need thereof, comprising:

- a) selecting a subject on the basis of the subject having vasculitis; and
- b) providing said subject with a therapeutically effective amount of an IL-17 binding molecule, wherein said IL-17 binding molecule comprises
 - i) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
 - ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
 - iii) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;

- iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- v) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- vii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or
- viii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6,

wherein providing said a therapeutically effective amount of an IL-17 binding molecule to said subject results in treatment of vasculitis.

Disclosed herein is also an IL-17 binding molecule for use in the treatment of vasculitis, wherein said IL-17 binding molecule comprises,

- i) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- iii) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- v) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;

vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;

vii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or

viii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;

said use comprising

- a) selecting a subject on the basis of the subject having vasculitis; and
- b) providing said subject with a therapeutically effective amount of said IL-17 binding molecule.

In some embodiments of the disclosed methods, IL-17 binding molecules or uses, the IL-17 binding molecule is AIN457 (secukinumab). In further embodiments, the vasculitis is an autoimmune vasculitis or a large vessel vasculitis. In further embodiments, the vasculitis is isolated PMR. In further embodiments, the vasculitis is PMR associated with GCA. In further embodiments, the vasculitis is isolated GCA. In further embodiments, the vasculitis is GCA associated with PMR. In one embodiment, an additional agent for use in the disclosed methods or uses, or to be co-administered with a disclosed IL-17 binding molecule, is selected from the group consisting of prednisone, methotrexate, prednisolone, methylprednisone, methylprednisolone and deflazacort.

Disclosed herein is also a method of regulating the dose and/or frequency of providing an IL-17 binding molecule to a subject having vasculitis comprising: (a) measuring the concentration of one of the following in blood or tissue of the subject: free IL-17 protein, IL-17 mRNA, and/or Th17 cells; and (b) increasing the dose and/or frequency of the IL-17 binding molecule if the concentration is below a predetermined value and reducing the dose and/or frequency of the IL-17 binding molecule if the

concentration is above a predetermined value, thereby regulating the dose and/or frequency of providing the IL-17 binding molecule to the subject.

Disclosed herein is also an IL-17 binding molecule for use in the treatment of vasculitis in a subject, said use comprising: (a) measuring the concentration of one of the following in blood or tissue of the subject: free IL-17 protein, IL-17 mRNA, and/or Th17 cells; and (b) increasing the dose and/or frequency of the IL-17 binding molecule if the concentration is below a predetermined value and reducing the dose and/or frequency of the IL-17 binding molecule if the concentration is above a predetermined value, thereby regulating the dose and/or frequency of providing the IL-17 binding molecule to the subject.

Disclosed herein is also a method of selecting a subject having vasculitis for therapy with an IL-17 binding molecule comprising: (a) measuring the concentration of one of the following in blood or tissue of the subject: free IL-17 protein (i.e., unbound by the IL-17 binding molecule), IL-17 mRNA, and/or Th17 cells; and (b) selecting the subject for said therapy if the concentration exceed a control value, thereby selecting a subject having vasculitis for therapy with an IL-17 binding molecule

In some embodiments of the above methods, IL-17 binding molecules and uses, the control value is obtained from a derived from a person known not to have vasculitis. In some embodiments of the disclosed methods, the IL-17 binding molecule is AIN457 (secukinumab). In further embodiments, the vasculitis is autoimmune vasculitis or a large vessel vasculitis. In further embodiments, the vasculitis is isolated PMR. In further embodiments, the vasculitis is PMR associated with GCA. In further embodiments, the vasculitis is isolated GCA. In further embodiments, the vasculitis is GCA associated with PMR. In one embodiment, an additional agent for use in the disclosed methods or uses, or to be co-administered with a disclosed IL-17 binding molecule, is selected from the group consisting of prednisone, methotrexate, prednisolone, methylprednisone, methylprednisolone and deflazacort.

Combination Therapies for the Treatment of PMR and GCA

For the treatment of PMR and GCA, the IL-17 binding molecules may be administered as the sole active ingredient or in conjunction with, e.g., as an adjuvant to or in combination to, other agents, e.g., immunosuppressive or immunomodulating agents or other anti-inflammatory agents. For example, the IL-17 binding molecules may be used in combination with corticosteroids such as prednisone, prednisolone, methylprednisone, methylprednisolone and deflazacort; glucocorticoids, DMARD, e.g., Gold salts, sulphasalazine, antimalarias, aspirin, NSAIDs, methotrexate, D-penicillamine, azathioprine, mycophenolic acid, cyclosporine A, tacrolimus, sirolimus, minocycline, leflunomide, glucocorticoids; a calcineurin inhibitor, e.g., cyclosporin A or FK 506; a modulator of lymphocyte recirculation, e.g., FTY720 and FTY720 analogs; an mTOR inhibitor, e.g., rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, CCI779, Humira®, ABT578, AP23573 or TAFA-93; an ascomycin having immuno-suppressive properties, e.g., ABT-281, ASM981; corticosteroids such as prednisone, prednisolone, methylprednisone, methylprednisolone and deflazacort; cyclo-phos-phamide; alendronate, alfacalcidol (1-alpha OH vitamin D), hydroxychloroquine, abatacept, azathioprene; methotrexate; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; anti-thymocyte globulin; cyclophosphamide; filgrastim; 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28, CD40, CD45, CD58, CD80, CD86 or their ligands; monoclonal antibodies (e.g., agonistic or antagonistic antibodies) to cytokines such as IL-6, IL-15, LIF, IL-10, IFN γ , TNF α , IL-23, IL-1 β , IL-2, IL-12, IL-4, IL-8, IL-21, IL-18, IL-26, OSM, and TGF β , as well as other IL-1, IL-17 and TNF family members, other immunomodulatory compounds, e.g., a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g., at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (for ex. designated ATCC 68629) or a mutant thereof, e.g., LEA29Y; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or -3

antagonists, VCAM-4 antagonists or VLA-4 antagonists; or a chemotherapeutic agent, e.g. paclitaxel, gemcitabine, cisplatin, doxorubicin or 5-fluorouracil; TNF blockers, e.g., an anti-TNF agent, e.g., monoclonal antibodies to TNF, e.g. infliximab, adalimumab, Humira®, CDP870, or receptor constructs to TNF-RI or TNF-RII, e.g., Etanercept, PEG-TNF-RI; blockers of proinflammatory cytokines, an IL-1 blockers, e.g., Anakinra or IL-1 trap, a calcineurin inhibitor, a PKC inhibitor, e.g., sotrastaurin (AEB071), JAK1 and JAK2 inhibitors, pan JAK inhibitors, e.g., tetracyclic pyridone 6 (P6), 325, PF-956980, AAL160, , solumedrol, IL-6 blockers (e.g., tocilizumab); chemokines blockers, e.g., inhibitors or activators of proteases, e.g. metalloproteases, anti-CD20 antibodies, an anti-infectious agent, bone calcilytics, bone anabolics, and bone anti-resorptives, e.g., an anti-sclerostin antibody, such as BPS804, AMG785, AMG167, LY254156, a bisphosphonate such as alydrionate or zoledronic acid, e.g., Zometa®, PTH and PTH/PTHrP fragments, ActRIIA Fc-fusion proteins, anti-RANKL antibodies (e.g., Denosumab), Forteo® / Forsteo® (rhPTH (1-34), teriparatide), an injectable version of the human full-length peptide (PTH (1-84), Preos®/Preotact®, BA058 (BIM44058), a hPTH (1-31) amide analog (e.g., Ostabolin C), BN003, a PTH releaser (e.g., ronacaleret hydrochloride (SB-751689)), ronacaleret, an activin type IIA receptor-Fc fusion protein (e.g., ACE-011), Denosumab (AMG 162), calcium and Vitamin D.

Other agents for use in combination with the disclosed IL-17 binding molecules, e.g., IL-17 antibodies, e.g., AIN457, include MTI-MMP inhibitors (such as those disclosed in WO10/069074, which is incorporated by reference herein in its entirety), modulators of MIF (such as those disclosed in WO10/065491, which is incorporated by reference herein in its entirety), complement modulating agents (such as those disclosed in WO10/056399, which is incorporated by reference herein in its entirety), agents that inhibit the interactions of PF4 and RANTES (such as those disclosed in WO10/042548 (US20100093636), which are incorporated by reference herein in their entirety), agents that inhibit MIF binding to CXCR2 and CXCR4 and/or inhibit MIF-activation of CXCR2 and CXCR4 and/or inhibit the ability of MIF to form a homomultimer (such as those disclosed in WO09/117710 and WO09/117706, which are incorporated by reference herein in their entirety), and phenazine derivatives (such as those disclosed in

WO09/042114, which is incorporated by reference herein in its entirety). Other agents include anti IL-1 β antibodies or IL-1 β receptor antagonists, , e.g., Illaris® (canakinumab, ACZ885) or Anakinra.

In accordance with the foregoing the present disclosure provides in a yet further aspect: a method or use as defined herein comprising co-administration, e.g., concomitantly or in sequence (sequentially), of a therapeutically effective amount of an IL-17 binding molecule, e.g., an IL-17 antibody, e.g., AIN457, and at least one additional agent, said additional agent being a immuno-suppressive / immunomodulatory, anti-inflammatory chemotherapeutic or anti-infectious drug, e.g., as indicated above. In a preferred embodiment, the additional agent for use in the disclosed methods or uses, or to be co-administered with a disclosed IL-17 binding molecule, is selected from the group consisting of prednisone, methotrexate, prednisolone, methylprednisone, methylprednisolone and deflazacort.

In accordance with the foregoing the present disclosure provides in a yet further aspect: a therapeutic combination, e.g. a kit, comprising of a therapeutically effective amount of a) an IL-17 binding molecule, e.g., an IL-17 antibody, e.g. AIN457, and b) at least one additional agent selected from a immuno-suppressive / immunomodulatory, anti-inflammatory chemotherapeutic or anti-infectious drug, e.g., as indicated above. The kit may comprise instructions for its administration.

Where an IL-17 binding molecule is administered in conjunction with other immuno-suppressive / immunomodulatory, anti-inflammatory chemotherapeutic or anti-infectious therapy, dosages of the co-administered additional agent will of course vary depending on the type of co-drug employed, e.g., whether it is a steroid, DMARD, anti-TNF, IL-1 blocker or others, on the specific additional agent, on the condition being treated, and so forth.

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Examples

Example 1: The AIN457 Antibody Binds Human IL-17 with High Affinity and Neutralizes Human IL-6

Affinity of AIN457 for Human IL-17

Surface plasmon resonance measurements using the optical biosensor BIAcore® 2000 (BIAcore AB, Uppsala, Sweden) was used to determine kinetic binding parameters and levels of crossreactivity for AIN457 (secukinumab) (disclosed in US20090280131). After combining the titration series the average values from twelve sensorgrams are:

- $k_{on} = (4.1 \pm 0.1) \times 10^5$ 1/M s;
- $k_{off} = (3.8 \pm 0.5) \times 10^{-4}$ 1/s;
- $K_D = 122 \pm 22$ pM. (**Table 2**).

Table 2. Kinetic constants for the 1:1 binding of rec human IL-17 to AIN457

Conc [nM]	k_{on} [1/Ms]	k_{off} [1/s]	K_D [M]	Exp. IL-314
2	3.31E+05	3.36E-05	1.02E-10	Run 1
4	1.28E+05	3.78E-05	2.95E-10	
8	3.79E+05	1.86E-05	4.90E-11	
12	3.60E+05	3.00E-05	8.33E-11	
16	3.52E+05	5.70E-05	1.62E-10	
20	3.52E+05	4.15E-05	1.18E-10	
2	1.23E+06	1.97E-05	1.60E-11	Run 2
4	4.11E+05	1.20E-05	2.92E-11	
8	3.78E+05	4.54E-05	1.20E-10	
12	3.46E+05	5.13E-05	1.48E-10	
16	3.17E+05	5.95E-05	1.88E-10	
20	3.34E+05	5.01E-05	1.50E-10	
Mean	4.10E+05	3.80E-05	1.22E-10	n=12
SEM	7.73E+04	4.51E-06	2.21E-11	

Mean K_D calculated from individual entries (vertically), rather than by applying the equation $K_D = k_{off}/k_{on}$.

Neutralizing activity of culture supernatants

As disclosed in US20090280131, AIN457 (secukinumab) neutralizes human IL-6 production induced by huIL-17 in human dermal fibroblast with an IC_{50} of 2.1 ± 0.1 nM at a concentration of 1.87 nM huIL-17. Thus, AIN457 neutralizes IL-17 antigen at a molar ratio of about 1:1. The potency of AIN457 is comparable to that of huIL-17R/Fc and superior to that of a commercially available mouse anti-huIL-17 MAb (MAB 317 R&D System). More complete inhibition is observed with AIN457 than with IL-17R/Fc. This high binding affinity makes the AIN457 antibody particularly suitable for therapeutic applications as disclosed herein.

Example 2: Treatment of Subjects Having PMR with AIN457

Objectives:

The primary purpose of this study is to determine whether a single 3 mg/kg intravenous dose of AIN457 (secukinumab) or ACZ885 (canakinumab) effectively reduces the initial signs and symptoms of PMR in untreated subjects as measured by the polymyalgia rheumatica activity score (PMR-AS) (Leeb and Bird (2004) Ann. Rheum. Dis. 63:1279-1283). Secondary aims of this study are to investigate the duration of an observed clinical response to single dose treatment and the safety and tolerance of said treatment in this patient population.

Design:

The study design is shown in **Figure 1**. The study is a two-week, single-blinded, double-dummy, randomized, active-controlled, parallel group design, with a follow-up period up to a total study. The first part of the study will consist of a 7-day screening period, a baseline visit and an initial treatment period of 2 weeks. Patients will be randomized in a ratio of 1:1:1 to receive either a single intravenous dose on Day 1 of AIN457 (secukinumab) 3 mg/kg or ACZ885 (canakinumab) 3 mg/kg or daily oral doses of prednisone 20mg.

At Day 15, the randomized treatment will be unblinded to the investigator (although not to the blinded evaluator). After unblinding, the patient will be assessed

against the following criteria for partial and complete response.

A partial responder is defined as a patient with all of the following:

- >50% reduction in patient global assessment VAS compared with baseline
- Morning stiffness < 60 min

A complete responder is defined as a patient with all of the following:

- >70% reduction in patient global assessment VAS compared with baseline
- Morning stiffness < 30 min
- CRP < 1.0 mg/dl and/or ESR < 30 mm/1st hr

Patients who do not meet the criteria of partial response at Day 15 (i.e. non-responders) and who received prednisone on Day 1 will be discontinued from the study. Non-responders who received AIN457 or ACZ885 on Day 1 will start the non-responder cycle (visit 21) receiving a 20mg dose of prednisone or prednisolone followed by the standard steroid tapering.

The remaining patients who meet criteria as either partial or complete treatment responders will continue in the study. Responders in the steroid treatment arm will taper their steroids according to standard of care.

During the follow up period, patients will be observed at regular intervals for evidence of disease flare. Disease flare is defined as (patients must have all of these 3 features):

- Return of typical proximal muscle pain
- Morning stiffness > 60 min
- CRP > 1.0 mg/dl and/or ESR > 30 mm/1st hr

Patients with confirmed disease flare in the biologics arms will be eligible for one re-dose of the biologic previously received at study start, with any further flare of their disease resulting in a change to standard of care steroid treatment. Patients with confirmed disease flare during a steroid taper will be uptitrated according to the standard of care.

Patients will have a follow up-period of 154 days (starting on D15) or 4 months (112 days) after their last biologic dosing (AIN457 or ACZ885), whichever is the greater.

If a patient flares more than 3 times during this follow-up period then the patient will be discontinued from the study.

Inclusion criteria:

Patients must meet all of the following features:

- Patients ≥ 50 and ≤ 85 years of
- CRP > 1.0 mg/dl OR ESR > 30 mm/hr
- New bilateral shoulder and/or hip pain
- Early Morning stiffness > 60 min
- Duration of illness > 1 week
- A negative 5 U PPD skin test (≤ 5 mm induration) at screening

Exclusion criteria

- Active infection or current use of antibiotics
- Known HIV, HCV or HBV
- Previous therapy with methotrexate or other immunosuppressive agents within three months prior to baseline
- History of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix within five years prior to study entry
- Presence of rheumatoid arthritis or other inflammatory arthritic processes (features of GCA, spondyloarthropathies), connective tissue disease, drug-induced myopathies, endocrine disorders, neurological disorders, chronic pain syndromes, as assessed by base line screening including TSH, CK, RF, CCP, ANA, serum protein electrophoresis, urinalysis.

Investigational Drug:

This is a double dummy study dosing (vials will be reconstituted to an i.v. solution of 3mg/kg to be administered as an infusion) of AIN457 150 mg powder for i.v. infusion in vial or ACZ885 150 mg powder for i.v. infusion in vial. Glucose 5% solution for i.v. infusion will be used as placebo matching AIN457 and ACZ885 solutions.

Comparator drug:

Prednisone 20mg capsules and placebo capsules. The starting dose of 20 mg/day prednisone is chosen based on the current standard of care dosing range of 10-20 mg/day for the initial treatment of PMR (Salvarani et al, *supra*).

Duration of study and treatment:

Patient will have a maximum screening period of 7 days. Randomization will occur at D1 for a single blind dosing period of 15 days followed by a follow up-period of 154 days, or 4 months (112 days) after their last biologic dose, whichever is greater, and followed by unblinded re-dosing in the case of a disease flare.

Efficacy assessments

- Polymyalgia Rheumatica (PMR) Activity Score (PMR-AS) components:
 - CRP (mg/dl)
 - Morning stiffness (min)
 - Ability to elevate upper limbs (scored on a 4-point scale; 3 = none, 2 = below shoulder girdle, 1 = up to shoulder girdle, 0 = above shoulder girdle)
 - Patient pain VAS (mm)
 - Patient global assessment VAS (mm)
 - Physician global assessment VAS (mm)
- Health Assessment Questionnaire-Disability Index (HAQ-DI)
- Short Form-36 (SF-36)
- Erythrocyte sedimentation rate (ESR)

Note: To improve enrollment, the exclusion criteria were modified to allow patients previously treated with steroids into the study if they have been withdrawn from steroids at least 3 months prior the screening visit. Previously, the protocol required that patients not have had any prior treatment for PMR.

Day 15 Results:

To date, 11 patients with untreated PMR have been enrolled in this ongoing study, including one patient that was discontinued due to a pharmacy error (no treatment given). These randomized patients received a single dose ACZ885 (n = 4), AIN457 (n = 3) or daily treatment with prednisone (n = 3). At day 15 the patient's treatment allocation is unblinded. The primary outcome measure for this study is the Polymyalgia Rheumatica Activity Score (PMR-AS; Leeb BF, Bird HA (2004) A disease activity score for polymyalgia rheumatic. Ann Rheum Dis;63:1279-1283) recorded at base line and again at Day 15 of treatment. This score is a weighted composite of 5 separate disease activity parameters, including the serum C-reactive protein, visual analog scales for patient perception of pain and for the physician's global assessment, duration of morning stiffness, and the ability to elevate the arms as follows:

Calculation of disease activity: Polymyalgia Rheumatica-Activity Score (PMR-AS)

CRP (mg/dl) + VASpain (0-10) + VASpga (0-10) + [MST (min) x 0.1] + EUL (3-0)

- **CRP** (mg/dl)
- **VASpain** = Patient visual analog scale pain
- **VASpga** = Physician's visual analog scale global assessment
- **MST** = Morning stiffness (min)
- **EUL** = Elevation of upper limbs (3 = none, 2 = below shoulder girdle, 1 = up to shoulder girdle, 0 = above shoulder girdle)

The overall mean percentage change from baseline (estimated from a model) for each of the 3 treatment groups are as follows: Prednisone 94%, ACZ885 42%, AIN457 43%. Further detail of the individual patient responses to treatment are shown in **Figure 2**. In the prednisone treatment arm, all patients showed a marked reduction in the PMR-AS compared to baseline measurements. In the ACZ885 treatment arm, 2 of the 4 patients showed reduction of the PMR-AS. In the AIN457 treatment arm, 1 patient out of 3 showed a reduction in the PMR-AS.

Further detail of treatment effects is revealed from the PMR-AS components (**Figure 3**). In the prednisone treatment arm, consistent reductions in the different PMR-AS components are noted in the individual patients with the exception of one patient's CRP value. In the biologics treatment arms, there is more heterogeneity in the responses of the various PMR-AS components. For example, consistent marked reductions in serum C-reactive protein levels are seen in the 3 AIN457-treated patients, but mixed responses in the remainder of the PMR-AS components. In the ACZ885 treated patients, variability is observed in all of the different PMR-AS components, with marked reductions in some components and minimal or no reductions in others.

WHAT IS CLAIMED IS:

1. A method of treating vasculitis in a subject comprising, administering a therapeutically effective amount of an IL-17 binding molecule to a subject in need thereof, wherein said IL-17 binding molecule comprises

- a) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- b) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- c) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- d) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- e) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- f) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- g) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or
- h) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6.

2. An IL-17 binding molecule for use in the treatment of vasculitis, wherein said IL-17 binding molecule comprises

- a) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;

- b) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- c) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- d) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- e) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- f) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- g) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or
- h) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6.

3. Use of an IL-17 binding molecule for the preparation of a medicament for the treatment of vasculitis, wherein said IL-17 binding molecule comprises

- a) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- b) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- c) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- d) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;

e) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;

f) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;

g) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or

h) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6.

4. The method of claim 1, the IL-17 binding molecule of claim 2 or the use of claim 3, wherein said IL-17 binding molecule is AIN457 (secukinumab).

5. The method, the IL-17 binding molecule or the use of claim 4, wherein said vasculitis is an autoimmune vasculitis or a large vessel vasculitis.

6. The method, the IL-17 binding molecule or the use of claim 4, wherein said vasculitis is isolated PMR.

7. The method, the IL-17 binding molecule or the use of claim 4, wherein said vasculitis is PMR associated with GCA.

8. The method, the IL-17 binding molecule or the use of claim 4, wherein said vasculitis is isolated GCA.

9. The method, the IL-17 binding molecule or the use of claim 4, wherein said vasculitis is GCA associated with PMR.

10. The method of claim 4 further comprising, administering an additional agent selected from the group consisting of prednisone, methotrexate, prednisolone, methylprednisone, methylprednisolone and deflazacort.

11. The use of claim 4 further comprising, an additional agent selected from the group consisting of prednisone, methotrexate, prednisolone, methylprednisone, methylprednisolone and deflazacort.

12. The IL-17 binding molecule of claim 4, wherein said IL-17 binding molecule is co-administered in combination with an additional agent selected from the group consisting of prednisone, methotrexate, prednisolone, methylprednisone, methylprednisolone and deflazacort.

13. A method of treating vasculitis in a subject in need thereof, comprising:

a) selecting a subject on the basis of the subject having vasculitis; and

b) providing said subject with a therapeutically effective amount of an IL-17 binding molecule, wherein said IL-17 binding molecule comprises

i) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;

ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;

iii) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;

iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;

v) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;

vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;

vii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or

viii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6,

wherein providing said a therapeutically effective amount of an IL-17 binding molecule to said subject results in treatment of vasculitis.

14. An IL-17 binding molecule for use in the treatment of vasculitis, wherein said IL-17 binding molecule comprises,

- i) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8;
- ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10;
- iii) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10;
- iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3;
- v) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;
- vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13;
- vii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or

viii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6;

said use comprising

- a) selecting a subject on the basis of the subject having vasculitis; and
- b) providing said subject with a therapeutically effective amount of said IL-17 binding molecule.

15. The method of claim 13 or the IL-17 binding molecule of claim 14, wherein said IL-17 binding molecule is AIN457 (secukinumab).

16. The method or the IL-17 binding molecule of claim 15, wherein said vasculitis is autoimmune vasculitis or a large vessel vasculitis.

17. The method or the IL-17 binding molecule of claim 15, wherein said vasculitis is isolated PMR.

18. The method or the IL-17 binding molecule of claim 15, wherein said vasculitis is PMR associated with GCA.

19. The method or the IL-17 binding molecule of claim 15, wherein said vasculitis is isolated GCA.

20. The method or the IL-17 binding molecule of claim 15, wherein said vasculitis is GCA associated with PMR.

21. The method of claim 15 further comprising, administering an additional agent selected from the group consisting of prednisone, prednisolone, methylprednisone, methylprednisolone, methotrexate, and deflazacort.

22. The IL-17 binding molecule of claim 15, wherein said IL-17 binding molecule is provided in combination with an additional agent selected from the group consisting of prednisone, prednisolone, methylprednisone, methylprednisolone, methotrexate, and deflazacort.

23. A method of regulating the dose and/or frequency of providing an IL-17 binding molecule to a subject having vasculitis comprising:

(a) measuring the concentration of one of the following in blood or tissue of the subject: free IL-17 protein, IL-17 mRNA, and/or Th17 cells; and

(b) increasing the dose and/or frequency of the IL-17 binding molecule if the concentration is below a predetermined value and reducing the dose and/or frequency of the IL-17 binding molecule if the concentration is above a predetermined value, thereby regulating the dose and/or frequency of providing the IL-17 binding molecule to the subject.

24. An IL-17 binding molecule for use in the treatment of vasculitis in a subject, said use comprising:

(a) measuring the concentration of one of the following in blood or tissue of the subject: free IL-17 protein, IL-17 mRNA, and/or Th17 cells; and

(b) increasing the dose and/or frequency of the IL-17 binding molecule if the concentration is below a predetermined value and reducing the dose and/or frequency of the IL-17 binding molecule if the concentration is above a predetermined value, thereby regulating the dose and/or frequency of providing the IL-17 binding molecule to the subject.

25. A method of selecting a subject having vasculitis for therapy with an IL-17 binding molecule comprising:

(a) measuring the concentration of one of the following in blood or tissue of the subject: free IL-17 protein (i.e., unbound by the IL-17 binding molecule), IL-17 mRNA, and/or Th17 cells; and

(b) selecting the subject for said therapy if the concentration exceed a control value, thereby selecting a subject having vasculitis for therapy with an IL-17 binding molecule.

26. The method of claim 23 or 25, or the IL-17 binding molecule of claim 24, wherein said IL-17 binding molecule is AIN457 (secukinumab).

27. The method or the IL-17 binding molecule of claim 26, wherein said vasculitis is an autoimmune vasculitis or a large vessel vasculitis.

28. The method or the IL-17 binding molecule of claim 26, wherein said vasculitis is isolated PMR.

29. The method or the IL-17 binding molecule of claim 26, wherein said vasculitis is PMR associated with GCA.

30. The method or the IL-17 binding molecule of claim 26, wherein said vasculitis is isolated GCA.

31. The method or the IL-17 binding molecule of claim 26, wherein said vasculitis is GCA associated with PMR.

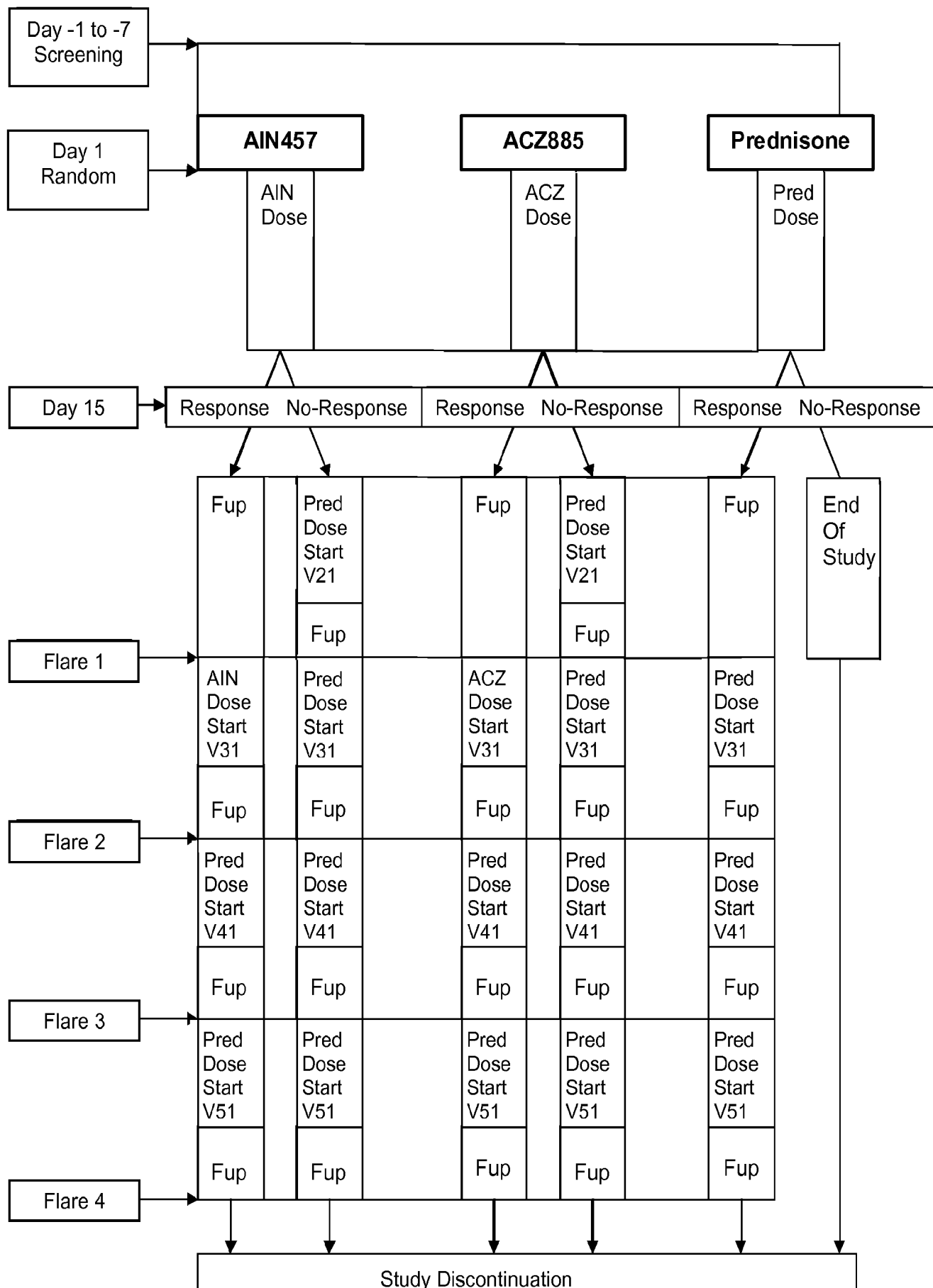


Figure 2

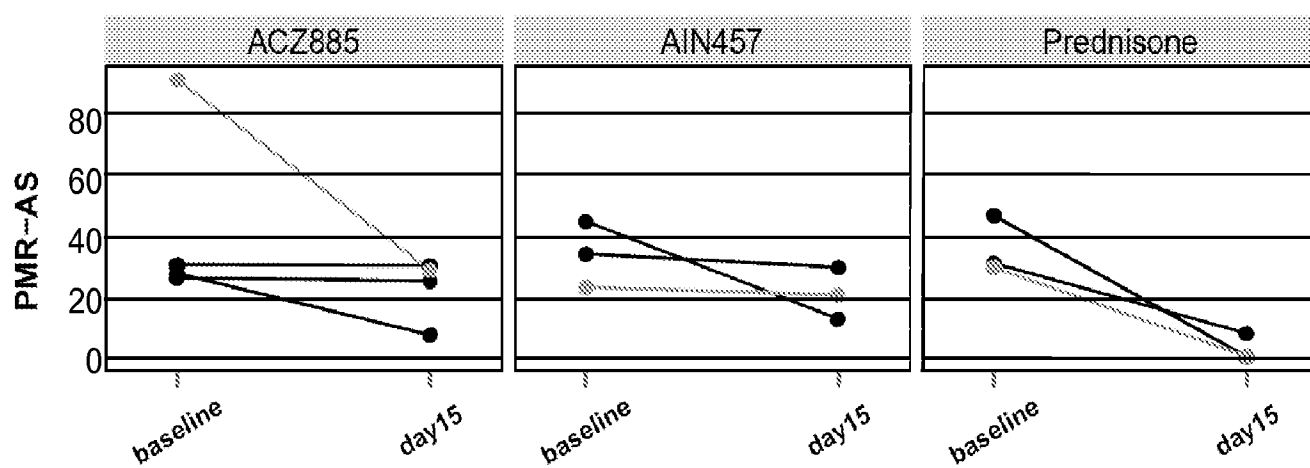
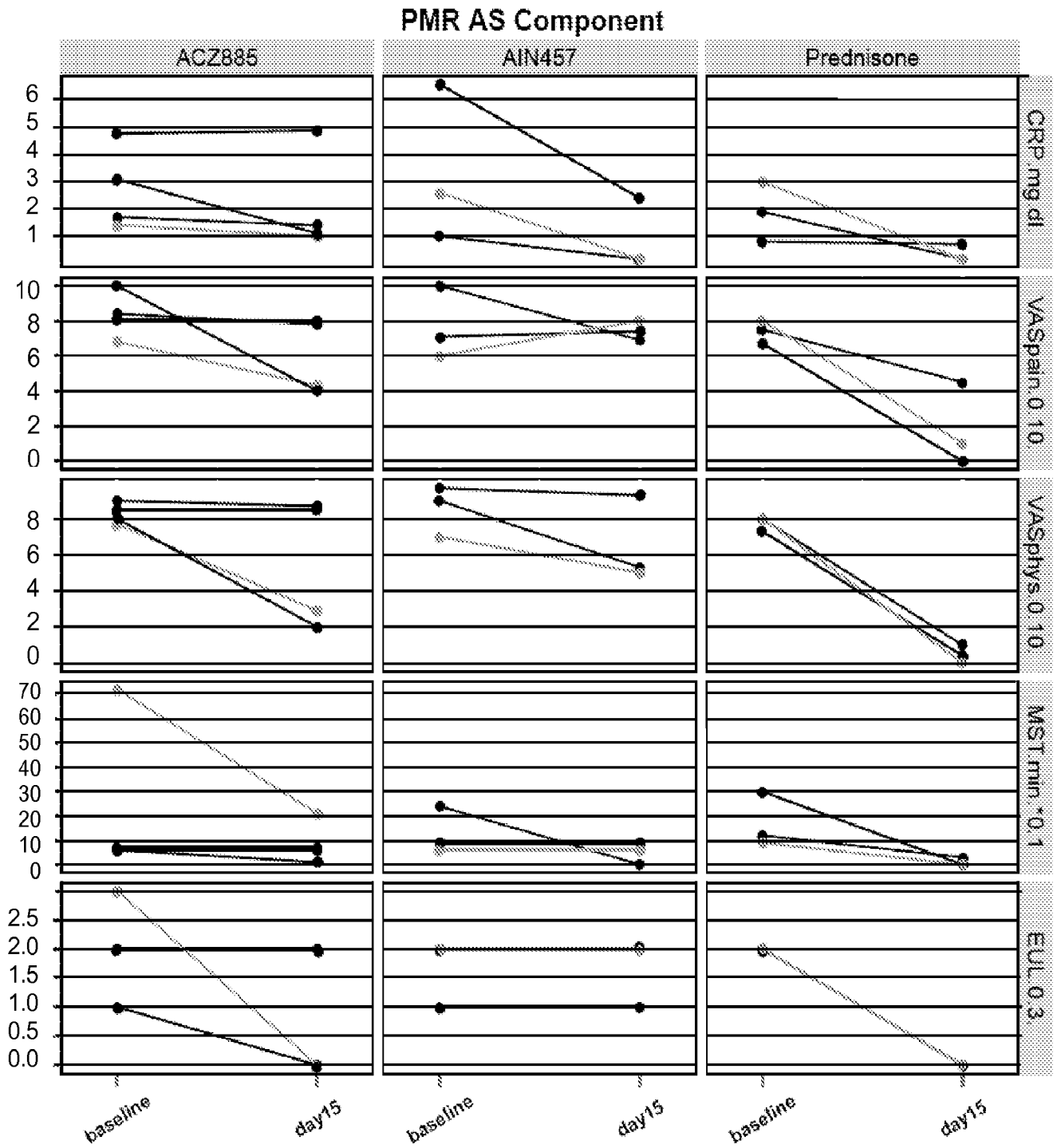


Figure 3.



INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/029002

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K16/24 A61K39/395 A61P37/00
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)

C07K A61K

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, BIOSIS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	YANG JI ET AL: "Th17 and Natural Treg Cell Population Dynamics in Systemic Lupus Erythematosus", ARTHRITIS & RHEUMATISM, vol. 60, no. 5, May 2009 (2009-05), pages 1472-1483, XP002677659, ISSN: 0004-3591 abstract page 1481, right-hand column, paragraph 3 page 1483, left-hand column, paragraph 3 page 1476, right-hand column page 1481, right-hand column, paragraph 1 - paragraph 3 page 1482, left-hand column, paragraph 1 - paragraph 2 ----- -/-	1-31



Further documents are listed in the continuation of Box C.



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

13 June 2012

Date of mailing of the international search report

27/06/2012

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Fax: (+31-70) 340-3016

Authorized officer

Irion, Andrea

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/029002

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Y	WEYAND CORNELIA M ET AL: "IFN-gamma and IL-17: the two faces of T-cell pathology in giant cell arteritis", CURRENT OPINION IN RHEUMATOLOGY, vol. 23, no. 1, January 2011 (2011-01), pages 43-49, XP009160117, ISSN: 1040-8711 abstract page 46, left-hand column, paragraph 2 - page 47, left-hand column, paragraph 2 -----	1-31
Y	GAN POH-YI ET AL: "Th17 Cells Promote Autoimmune Anti-Myeloperoxidase Glomerulonephritis", JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, vol. 21, no. 6, June 2010 (2010-06), pages 925-931, XP002677661, ISSN: 1046-6673 page 925, left-hand column, paragraph 1 abstract page 926, left-hand column, paragraph 2 page 928, right-hand column, paragraph 1 -----	1-31
Y	NOGUEIRA ESTELA ET AL: "Serum IL-17 and IL-23 levels and autoantigen-specific Th17 cells are elevated in patients with ANCA-associated vasculitis", NEPHROLOGY DIALYSIS TRANSPLANTATION, vol. 25, no. 7, July 2010 (2010-07), pages 2209-2217, XP002677662, ISSN: 0931-0509 abstract page 2215, left-hand column, paragraph 2 page 2215, right-hand column, paragraph 3 page 2216, right-hand column, paragraph 2 ----- -/--	1-31

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/029002

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HUEBER WOLFGANG ET AL: "Effects of AIN457, a Fully Human Antibody to Interleukin-17A, on Psoriasis, Rheumatoid Arthritis, and Uveitis", SCIENCE TRANSLATION MEDICINE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, US, vol. 2, no. 52 / Article No.: 52ra72, 1 October 2010 (2010-10-01), pages 1-9, XP009155660, ISSN: 1946-6234 the whole document	1-31
Y	----- WO 2006/013107 A1 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; DI PADOVA FRANCO E [CH];) 9 February 2006 (2006-02-09) the whole document page 23, paragraph 3	1-31
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A	----- WO 2008/047134 A2 (UCB PHARMA SA [BE]; ADAMS RALPH [GB]; POPPLEWELL ANDREW GEORGE [GB]; R) 24 April 2008 (2008-04-24) the whole document -----	1-31

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2012/029002

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. (means)

☒

 on paper
 - ☒

 in electronic form
 - b. (time)

☒

 in the international application as filed
 - ☒

 together with the international application in electronic form
 - ☐

 subsequently to this Authority for the purpose of search
2.

☐

 In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/029002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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