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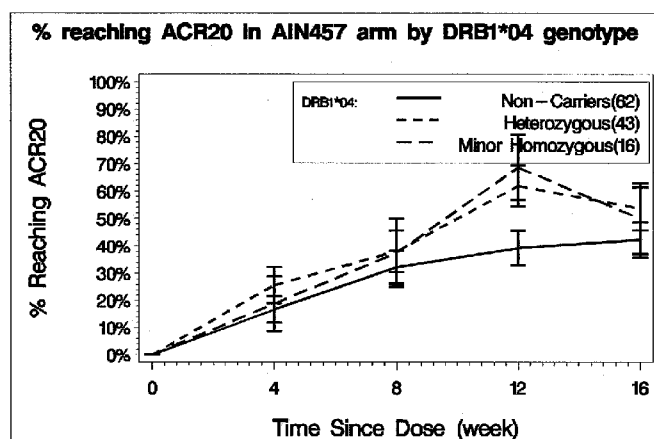
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(54) Title: PREDICTIVE METHODS AND METHODS OF TREATING ARTHRITIS USING IL-17 ANTAGONISTS

Figure 1



(57) Abstract: The disclosure is directed to novel predictive methods and personalized therapies for treating rheumatoid arthritis (RA). Specifically, the disclosure relates to predicting the likelihood of that a patient having RA will clinically respond to treatment with an IL-17 binding molecule, e.g., an IL-17 antibody, such as secukinumab.

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PREDICTIVE METHODS AND METHODS OF TREATING ARTHRITIS USING IL-17 ANTAGONISTS

This disclosure claims priority to US Provisional Patent Application No. 61/422,521, filed December 13, 2010, the disclosure of which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

The disclosure is directed to novel predictive methods and personalized therapies for treating rheumatoid arthritis (RA). Specifically, the disclosure relates to predicting the likelihood of that a patient having RA will clinically respond to treatment with an IL-17 antagonist, e.g., an IL-17 antibody, such as the AIN457 antibody (which is also known as “secukinumab”).

BACKGROUND OF THE DISCLOSURE

The human leukocyte antigen (HLA) genes within the class II region of the major histocompatibility complex (MHC) are the most important genetic risk factor for RA. (Holoshitz (2010) *Current Opinion in Rheumatology* 22:293–298). HLA-DRB1 alleles encoding the shared epitope (SE) confer higher risk for RA development (Gonzalez-Gay et al. (2002) *Sem. Arthritis. Rheum.* 31:355-60; Fries et al. (2002) *Arthritis and Rheumatism* 46:2320-29; van der Helm-van Mil et al. (2006) *Arthritis and Rheum.* 54:1117-21). The SE, an epitope of amino acid sequence R(Q)⁷⁰ K/R R AA⁷⁴, is found at position 70-74 in the third hypervariable region of the DRB1 chain. (Feitsma et al. (2010) *Arthritis and Rheum.* 62:117-25). SE-containing HLA-DRB1 alleles predispose to anti-citrullinated protein antibody (ACPA) + RA disease, and the SE epitope is exclusively associated with ACPA+ RA (de Vries et al. (2005) *J. Autoimmunity* 25:21-25). It has been theorized that citrullinated peptides processed from citrullinated proteins in the synovial fluid of RA patients (e.g., citrullinated vimentin) are recognized by T-cells expressing the products of SE-containing HLA-DRB1 alleles, leading to the production of ACPAs. (Gregersen et al. (1987) *Arthritis Rheum.* 30:1205-13). Thus, SE-containing HLA-

DRB1 alleles are generally understood to contribute to the production of autoantibodies, i.e., ACPA, rather than independently contributing to the progression of RA (van der Helm-van Mil et al., *supra*). However, a recent *in vitro* study indicates that SE may function as an immunostimulatory ligand that enhances IL-6 production and Th17 differentiation, while inhibiting the generation of Treg cells. (De Almeida et al (2010) J. Immunol 185:1927-34). De Almeida et al. show that SE-activated dendritic cells increase IL-17 production in CD4+ T cells; the SE may be involved in direct immune dysregulation via T cell polarization.

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic autoimmune disease of unknown etiology. It is characterized by symmetric synovitis leading to cartilage damage and joint destruction and can be complicated by numerous extra-articular manifestations. Given the presence of autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), RA is considered an autoimmune disease. RA is generally a progressive disease with functional status decline, significant morbidity and premature mortality seen in established RA. The goal of long-term RA treatment is disease remission. Disease-modifying antirheumatic drugs (DMARDs), a heterogeneous collection of agents grouped by use and convention, are the first line of treatment for RA patients. DMARDs, most often methotrexate (MTX), are prescribed upon disease diagnosis (i.e., early RA), usually before the development of erosive disease and the deformities seen in established RA. Unfortunately, only about 2/3 of patients respond to DMARDs, and DMARDs only partially control established RA disease. DMARDs also have many adverse effects (e.g., liver damage, bone marrow suppression and severe lung infection) that limit their prolonged use. Anti-TNF biological agents (Cimzia®, Enbrel®, Humira®, Remicade®, Simponi®) are the second line of treatment for RA patients, being used in DMARD-failure and DMARD-inadequate responder patients. A TNF inhibitor is often combined with MTX (or another DMARD) to aggressively treat established RA. Unfortunately, 30 – 40% of patients with established RA fail to respond to TNF- α antagonists and the majority of those that respond initially do not achieve complete remission or lose response over time. Concerns have also been raised about the short and long-term tolerability and safety of chronic biologic treatment, most notably the reactivation of serious infections (e.g., tuberculosis infections), liver toxicity, increased cardiovascular disease, induction (or exacerbation of) demyelinating conditions, and increased incidence of malignancy due to TNF-

alpha antagonism. M. Khraishi (2009) *J. Rheumatol Suppl.* 82:25-32; Salliot et al. (2009) *Ann. Rheum. Dis.* 68:25-32.

Given the aforementioned problems with current RA therapy, there is a need to develop methods of treating RA that first identify those patients most likely to benefit from a chosen RA treatment.

BRIEF SUMMARY OF THE DISCLOSURE

Secukinumab, a new biological in clinical development for RA, is a high-affinity fully human monoclonal anti-human antibody that inhibits Interleukin-17A activity. In an RA proof-of-concept (PoC) study, patients with active RA who were on a stable dose of MTX were dosed in rising single and then 2 doses (21 days apart) with secukinumab at 1mg/kg, 3mg/kg and 10mg/kg intravenously. Hueber et al. (2010) *Sci. Transl. Med.* 2(52):52-72. Treatment with secukinumab resulted in rapid improvement of the clinical manifestations of RA in many patients compared to placebo. These data provide evidence that neutralization of IL-17A is likely to be efficacious in RA patients with active RA. However, since patient response to biological treatment is variable and it is desirable to avoid providing drug to patients who will be resistant thereto, we have sought methods of treating RA that first identify those patients most likely to respond favorably to antagonism of IL-17. Therefore, provided herein are novel predictive methods and personalized therapies for treating RA that maximize the benefit and minimize the risk of IL-17 antagonism in the RA population by identifying those patients most likely to respond favorably to antagonism of IL-17 during treatment of RA. This finding is based, in part, on the determination that RA patients having a SE, an allele in the HLA-DRB1*SE allelic group, or an allele in the HLA-DRB1*04 allelic group display improved response to treatment with an IL-17 antagonist, i.e., secukinumab.

Accordingly, it is one object of the disclosure to provide methods of identifying patients who are more likely to respond to treatment of RA with an IL-17 antagonist, e.g., an IL-17 antibody, such as the AIN1457 antibody (secukinumab) by determining whether the patient has a SE, an allele in the HLA-DRB1*SE allelic group, or an allele in the HLA-DRB1*04 allelic group.

It is another object of the disclosure to provide methods of determining the likelihood that an RA patient will respond to treatment with an IL-17 antagonist, e.g., an IL-17 antibody, such as secukinumab, by determining whether the patient has a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1* SE allelic group.

It is another object of the disclosure to provide methods of treating RA, by administering the patient a therapeutically effective amount of an IL-17 antagonist, e.g., an IL-17 antibody, such as secukinumab, provided that the patient has a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1* SE allelic group.

Based upon the above objects and discoveries, disclosed herein are various methods of predicting the likelihood that a patient having rheumatoid arthritis (RA) will respond to treatment with an IL-17 antagonist, e.g., secukinumab. In some embodiments, these methods comprise assaying a biological sample from the patient for the presence or absence of a SE, at least one allele in the HLA-DRB1*04 allelic group, or at least one allele in the HLA-DRB1*SE allelic group (e.g., using an automatic analyzer), wherein the presence of a SE, at least one allele in the HLA-DRB1*04 allelic group, or at least one allele in the HLA-DRB1*SE allelic group is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of a SE, at least one allele in the HLA-DRB1*04 allelic group, or at least one allele in the HLA-DRB1*SE allelic group is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.

Disclosed herein are also kits for use in the described methods, e.g., for use in predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist, e.g., secukinumab, kits for use in treating a patient having RA, and kits comprising at least one probe capable of detecting the presence or absence of a SE, at least one allele in the HLA-DRB1*04 allelic group, or at least one allele in the HLA-DRB1*SE allelic group for predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist, e.g., secukinumab.

Disclosed herein are also various methods of treating RA. In some embodiments, these methods comprise assaying a biological sample from a RA patient for the presence or absence of a SE, at least one allele in the HLA-DRB1*04 allelic group, or at least one allele in the HLA-DRB1*SE allelic group; and administering a therapeutically effective amount of an IL-17 antagonist, e.g., secukinumab to the RA patient if the biological sample has the presence of a SE,

at least one allele in the HLA-DRB1*04 allelic group or at least one allele in the HLA-DRB1*SE allelic group.

Disclosed herein are also various methods of selectively treating a patient having RA. In some embodiments, these methods comprise determining whether a biological sample from the patient has the presence or absence of a SE, at least one allele in the HLA-DRB1*04 allelic group, or at least one allele in the HLA-DRB1*SE allelic group; and administering a therapeutically effective amount of an IL-17 antagonist, e.g., secukinumab to the RA patient if the biological sample has the presence of a SE, at least one allele in the HLA-DRB1*04 allelic group, or at least one allele in the HLA-DRB1*SE allelic group.

Disclosed herein are also various methods of treating an RA patient. In some embodiments, these methods comprise receiving data regarding the presence or absence in a biological sample obtained from said patient of a SE, at least one allele in the HLA-DRB1*04 allelic group, or at least one allele in the HLA-DRB1*SE allelic group; and administering an IL-17 antagonist, e.g., secukinumab to the patient if said received data indicates that the patient has a SE, at least one allele in the HLA-DRB1*04 allelic group, or at least one allele in the HLA-DRB1*SE allelic group.

Disclosed herein are also various methods for determining the responsiveness of a patient having RA to treatment with an IL-17 antagonist, e.g., secukinumab. In some embodiments, these methods comprise performing an assay on a biological sample from the patient to determine the presence or absence of a SE, at least one allele in the HLA-DRB1*04 allelic group, or at least one allele in the HLA-DRB1*SE allelic group; and assigning the patient as responsive to treatment with the IL-17 antagonist, e.g., secukinumab if the presence of a SE, at least one allele in the HLA-DRB1*04 allelic group, or at least one allele in the HLA-DRB1*SE allelic group is detected.

Disclosed herein are also methods for producing a transmittable form of information for use in predicting the responsiveness of a patient having RA to treatment with an IL-17 antagonist. In some embodiments, these methods comprise assaying a biological sample from the patient for the presence or absence of a SE, at least one allele in the HLA-DRB1*04 allelic group, or at least one allele in the HLA-DRB1*SE allelic group; and embodying the result of the assaying step in a transmittable form of information.

In some embodiments, the IL-17 antagonist is selected from the group consisting of: a) secukinumab; b) an IL-17 antibody that binds to an epitope of IL-17 comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129; c) an IL-17 antibody that binds to an epitope of IL-17 comprising Tyr43, Tyr44, Arg46, Ala79, Asp80; d) an IL-17 antibody that binds to an epitope of an IL-17 homodimer having two mature IL-17 protein chains, said epitope comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129 on one chain and Tyr43, Tyr44, Arg46, Ala79, Asp80 on the other chain; e) an IL-17 antibody that binds to an epitope of an IL-17 homodimer having two mature IL-17 protein chains, said epitope comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129 on one chain and Tyr43, Tyr44, Arg46, Ala79, Asp80 on the other chain, wherein the IL-17 binding molecule has a K_D of about 100-200 pM, and wherein the IL-17 antagonist has an *in vivo* half-life of about 4 weeks; and f) an IL-17 antibody that comprises an antibody selected from the group consisting of: 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; and 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.

In a preferred embodiment, the IL-17 antagonist is an IL-17 binding molecule, preferably a human antibody, most preferably secukinumab.

Additional methods, uses, kits, and probes are provided in the the following description and appended claims. Further features, advantages and aspects of the present disclosure will become apparent to those skilled in the art from the following description and appended claims. It should be understood, however, that the following description and specific examples, while indicating preferred embodiments of the disclosure, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed patient matter will become readily apparent to those skilled in the art from reading the following.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the effect of HLA-DRB1*04 alleles on ACR20 response at week 12 in all patients randomized to secukinumab at baseline.

Figure 2 shows the effect of of HLA-DRB1*04 alleles on ACR50 at week 12 & 16 in all patients randomized to secukinumab at baseline.

Figure 3 shows the effect of HLA-DRB1*04 alleles on DAS28 score at week 12 & 16 in all patients randomized to secukinumab at baseline.

Figure 4 shows the effect of HLA-DRB1*04 alleles on ACR50 from week 12 to week 52 in all patients randomized to secukinumab at baseline.

Figure 5 shows the effect of HLA-DRB1*04 alleles on ACR20 from week 12 to week 52 in all patients randomized to secukinumab at baseline.

Figure 6 shows the effect of HLA-DRB1*04 alleles on DAS28 score from week 12 to week 52 in all patients randomized to secukinumab at baseline.

Figure 7 shows the effect of HLA-DRB1*04 alleles on ACR50 from week 12 to week 52 in secukinumab-treated patients defined as responders (ACR20) at week 16.

Figure 8 shows the effect of HLA-DRB1*04 alleles on ACR20 from week 12 to week 52 in secukinumab-treated patients defined as responders (ACR20) at week 16.

Figure 9 shows the effect of HLA-DRB1*04 alleles on DAS28 score from week 12 to week 52 in secukinumab-treated patients defined as responders (ACR20) at week 16.

Figure 10 shows the effect of HLA-DRB1*04 alleles on ACR50 from week 12 to week 52 in all patients randomized to placebo at baseline.

Figure 11 shows the effect of HLA-DRB1*04 alleles on ACR20 from week 12 to week 52 in all patients randomized to placebo at baseline.

Figure 12 shows the effect of HLA-DRB1*04 alleles on DAS28 score from week 12 to week 52 in all patients randomized to placebo at baseline.

Figure 13 shows the effect of HLA-DRB1*04 alleles on ACR50 from week 16 to week 52 in patients randomized to placebo at baseline who were not treated with anti-TNF before.

Figure 14 shows the effect of HLA-DRB1*04 alleles on ACR20 from baseline to week 52 in patients randomized to placebo at baseline who were not treated with anti-TNF before.

Figure 15 shows the effect of HLA-DRB1*04 alleles on DAS28 score from baseline to week 52 in patients randomized to placebo at baseline who were not treated with anti-TNF before.

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 “administering” in relation to a compound, e.g., an IL-17 binding molecule or an anti-rheumatic agent, is used to refer to delivery of that compound to a patient by any route.

The phrase “active rheumatoid arthritis” or “active RA” is used to mean RA with visible signs and symptoms (e.g., swelling, difficulty in flexion, etc.).

The term “assaying” is used to refer to the act of identifying, screening, probing or determining, which act may be performed by any conventional means. For example, a sample may be assayed for the presence of a particular marker by using an ELISA assay, a Northern blot, imaging, etc. to detect whether that marker is present in the sample. The terms “assaying” and “determining” contemplate a transformation of matter, e.g., a transformation of a biological sample, e.g., a blood sample or other tissue sample, from one state to another by means of subjecting that sample to physical testing. Further, as used herein, the terms “assaying” and “determining” are used to mean testing and/or measuring. The phrase “assaying a biological sample from the patient for...” and the like is used to mean that a sample may be tested (either directly or indirectly) for either the presence or absence of a given factor or for the level of a particular factor. It will be understood that, in a situation where the presence of a substance denotes one probability and the absence of a substance denotes a different probability, then

either the presence or the absence of such substance may be used to guide a therapeutic decision. In the case of HLA typing, assaying may employ, e.g., various well-known methods of typing, including, e.g., serotyping, cellular typing, gene sequencing, phenotyping, haplotyping, etc.

As used herein, an “automatic analyzer” is any form of machine that can be used to determine the presence or absence of a SE, an allele in the HLA-DRB1*04 allelic group and/or an HLA-DRB1*SE allelic group. For example, a PCR machine, an automatic sequencer, a densitometer, a plate reader, a scintillation counter, etc.

The term “detecting” (and the like) means the act of extracting particular information from a given source.

The term “about” in relation to a numerical value x means $\pm 10\%$ unless the context dictates otherwise. 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.

“IL-17 antagonist” as used herein refers to a molecule capable of antagonizing (e.g., reducing, inhibiting, decreasing, delaying) IL-17 function, expression and/or signalling (e.g., by blocking the binding of IL-17 to the IL-17 receptor). Non-limiting examples of IL-17 antagonists include IL-17 binding molecules and IL-17 receptor binding molecules. In some embodiments of the disclosed methods, regimens, kits, processes, uses and compositions, an IL-17 antagonist is employed.

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 small molecules, IL-17 receptor decoys, and 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. Preferably the IL-17 binding molecule antagonizes (e.g., reduces, inhibits, decreases, delays) IL-17 function, expression and/or signalling. In some embodiments of the disclosed

methods, regimens, kits, processes, uses and compositions, an IL-17 binding molecule is employed.

By "IL-17 receptor binding molecule" is meant any molecule capable of binding to the human IL-17 receptor 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 receptor binding to IL-17 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 receptor binding molecules include small molecules, IL-17 decoys, and antibodies to the IL-17 receptor 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. Preferably the IL-17 receptor binding molecule antagonizes (e.g., reduces, inhibits, decreases, delays) IL-17 function, expression and/or signalling. In some embodiments of the disclosed methods, regimens, kits, processes, uses and compositions, an IL-17 receptor binding molecule is employed.

The term "antibody" as referred to herein includes whole antibodies and any 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 V_H) 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 V_L) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The V_H and V_L 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 V_H and V_L is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. 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. In some embodiments of the disclosed methods, regimens, kits, processes, uses and compositions, an antibody to IL-17 or the IL-17 receptor is employed.

The term "antigen-binding portion" of an antibody as used herein, refers to 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 V_L, V_H, 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 V_H and CH1 domains; a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody; a dAb fragment (Ward et al., 1989 Nature 341:544-546), which consists of a V_H domain; and an isolated complementarity determining region (CDR). Exemplary antigen binding sites include the CDRs of secukinumab as set forth in SEQ ID NOs:1-6 and 11-13 (**Table 4**), preferably the heavy chain CDR3. Furthermore, although the two domains of the Fv fragment, V_L and V_H, 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 V_L and V_H 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 "antibody". Single chain antibodies and antigen-binding portions are obtained using conventional techniques known to those of skill in the art. In some embodiments of the disclosed methods, regimens, kits, processes, uses and compositions, a single chain antibody or an antigen-binding portion of an antibody against IL-17 (e.g., secukinumab) or the IL-17 receptor is employed.

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 may be substantially free of other cellular material and/or chemicals. An isolated antibody that "specifically binds" IL-17 may, however, be cross-reactive with other antigens, such as IL-17 molecules from other species. In some embodiments of the

disclosed methods, regimens, kits, processes, uses and compositions, the IL-17 antagonist is an isolated antibody.

The term "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. In some embodiments of the disclosed methods, regimens, kits, processes, uses and compositions, the IL-17 antagonist is a monoclonal antibody.

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. 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. In some embodiments of the disclosed methods, regimens, kits, processes, uses and compositions, the IL-17 antagonist is a human antibody.

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 " K_D " 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. In some embodiments of the invention the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment

thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof) binds human IL-17 with a K_D of about 100-250 pM.

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 "subject" and "patient" 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.

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 affects 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 term "derivative", unless otherwise indicated, is used to define amino acid sequence variants, and covalent modifications of an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof) according to the present disclosure, e.g., of a specified sequence. A "functional derivative" includes a molecule having a qualitative biological activity in common with the disclosed IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen binding

fragment thereof). A functional derivative includes fragments and peptide analogs of an IL-17 antagonist as disclosed herein. Fragments comprise regions within the sequence of a polypeptide according to the present disclosure, e.g., of a specified sequence. Functional derivatives of the IL-17 antagonists disclosed herein preferably comprise V_H and/or V_L domains that have at least about 65%, 75%, 85%, 95%, 96%, 97%, 98%, or even 99% overall sequence identity with the V_H and/or V_L sequences of the IL-17 binding molecules disclosed herein (e.g., the V_H and/or V_L sequences of **Table 2**), or comprise CDRs that have at least about 65%, 75%, 85%, 95%, 96%, 97%, 98%, or even 99% overall sequence identity with the CDRs of the IL-17 antagonists (e.g., secukinumab) disclosed herein (e.g., have 1, 2, or 3 amino acid differences from the CDRs set forth in **Table 2**), and substantially retain the ability to bind the human IL-17 or, e.g., inhibit IL-6 production of IL-17 induced human dermal fibroblasts.

“Inhibit IL-6” as used herein refers to the ability of an IL-17 antagonist (e.g., secukinumab) 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 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 an IL-17 binding molecule 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. An IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof) as disclosed herein typically has an IC₅₀ 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 being measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts. In some embodiments of the disclosed methods, regimens, kits, processes, uses and compositions, IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof) and functional derivatives thereof have an IC₅₀ 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., inhibit 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.

The phrase "substantially identical" means that the relevant amino acid or nucleotide sequence (e.g., CDR(s), V_H, or V_L 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% or greater, e.g., 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher.

"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 Search Tool (BLAST) described by Altschul 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 include 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 the sequences according to the present disclosure. 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., inhibit IL-6 production of IL-17 induced human dermal fibroblasts. Amino acid sequence variants include substitutional variants (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), insertional variants (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) and deletional variants (those with one or more amino acids removed in a polypeptide according to the present disclosure).

As used herein, a "therapeutically effective amount" refers to an amount of an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment

thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof) that is effective, upon single or multiple dose administration to a patient (such as a human patient) at treating, preventing, preventing the onset of, curing, delaying, reducing the severity of, ameliorating at least one symptom of a disorder or recurring disorder, or prolonging the survival of the patient beyond that expected in the absence of such treatment. When applied to an individual active ingredient (e.g., an IL-17 antagonist, e.g., secukinumab) 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.

The term “treatment” or “treat” refer to both prophylactic or preventative treatment as well as curative or disease modifying treatment, including treatment of a 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 patient 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 patient beyond that expected in the absence of such treatment.

As used herein, the phrase “inflammatory arthritides” refers to a variety of conditions of the joints that involve the immune system and inflammation, and includes autoimmune disorders, e.g., rheumatoid arthritis. Non-limiting examples include seronegative spondyloarthropathies such as AS, Reiter’s syndrome, PsA, enteropathic arthritis, and other arthropathies such as RA, juvenile rheumatoid arthritis and systemic onset rheumatoid arthritis, crystalline arthritis (gout pseudogout, apatite gout), polymyalgia rheumatica, amyloid arthritis, pigment villonodular synovitis, synovial chondromatosis, hemophilic arthritis, and reactive synovitis. In some embodiments of the disclosed methods, regimens, uses, kits, and pharmaceutical compositions, the patient has an inflammatory arthritides.

The phrase “respond to treatment” is used to mean that a patient, upon being delivered a particular treatment, e.g., an IL-17 binding molecule, shows a clinically meaningful benefit from said treatment. In the case of RA, such benefit may be measured by a variety of criteria, e.g., ACR20, DAS28, ACR50, ACR70, DAS28_CRP, etc. The phrase “respond to treatment” is

meant to be construed comparatively, rather than as an absolute response. That is, a patient having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*04 allelic group (“carrier”) is predicted to have greater benefit from treatment with the IL-17 antagonist than a patient that does not have a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*04 allelic group. These carriers respond more favorably to treatment with the IL-17 antagonist, and may simply be said to “respond to treatment” with an IL-17 antagonist. The term “responsiveness” is a measure of the level of benefit of a given treatment.

The phrase “receiving data” is used to mean obtaining possession of information by any available means, e.g., orally, electronically (e.g., by electronic mail, encoded on diskette or other media), written, etc.

“Rheumatoid arthritis” or “RA” refers to a chronic, systemic inflammatory arthritis that may affect many tissues and organs, but principally attacks synovial joints. The 2010 ACR/EULAR criteria (found in Aletaha et al. (2010) *Ann. Rheum. Dis.* 69:1580-1588) may be used to classify a patient as having RA.

“C-reactive protein” and “CRP” refers to serum C-reactive protein, which is used as an indicator of the acute phase response to inflammation. The level of CRP in plasma may be given in any concentration, e.g., mg/dl, nmol/L. Levels of CRP may be measured by a variety of well known methods, e.g., radial immunodiffusion, electroimmunoassay, immunoturbidimetry, ELISA, turbidimetric methods, fluorescence polarization immunoassay, and laser nephelometry. Testing for CRP may employ a standard CRP test or a high sensitivity CRP (hs-CRP) test (i.e., a high sensitivity test that is capable of measuring low levels of CRP in a sample using laser nephelometry). Kits for detecting levels of CRP may be purchased from various companies, e.g., Calbiotech, Inc, Cayman Chemical, Roche Diagnostics Corporation, Abazyme, DADE Behring, Abnova Corporation, Aniera Corporation, Bio-Quant Inc., Siemens Healthcare Diagnostics, etc.

“High level of CRP” refers to an above normal CRP level as defined in the 2010 ACR/EULAR criteria (Aletaha et al. (2010) *Ann. Rheum. Dis.* 69:1580-88). According to the 2010 ACR/EULAR criteria, normal / abnormal CRP is based on local laboratory standards. Each local laboratory will employ a cutoff value for abnormal (high) CRP based on that laboratory’s rule for calculating normal maximum CRP. A physician generally orders a CRP test from a local laboratory, and the local laboratory reports normal or abnormal (low or high) CRP

using the rule that particular laboratory employs to calculate normal CRP. Thus, unless the context dictates otherwise, as used herein “high level of CRP” is not meant to denote a particular numerical value, as what is considered a normal CRP value will differ between laboratories and assays. “hsCRP” refers to the level of CRP in the blood as measured by high sensitivity CRP testing.

“Erythrocyte sedimentation rate”, “ESR”, “sedimentation rate”, and “sedrate” refer to the rate of sedimentation of erythrocytes in a patient sample. An ESR reflects plasma viscosity and the presence of acute phase proteins, and is normally reported in “mm/hr”. ESR is performed by measuring the distance that red blood cells precipitate in a tube over time. Typical ESR testing methods utilize the Westergren test, the Zeta Sedimentation Rate (ZSR) test and the Wintrobe test. Moseley and Bull (1982) Clin. Lab Haematol. 4:169-78; Miller et al. (1983) Br Med J (Clin Res Ed) 286 (6361):266, Wetteland et al. (1996) J. Intern. Med. 240 (3): 125–310, incorporated by reference herein in their entirety. Commercial kits for measuring ESR are available from, e.g., ARKRAY USA, BD Diagnostic Systems, and Poly Med Co. Inc. ESR instruments may be found, e.g. in US Patent 6974701, and from various companies, such as Steellex Scientific, Nicesound Electronics Co., Globe Scientific Inc., Alifax, AnalysisInstrument AB, Streck Laboratories, PolyMed Co. Inc., and Quantimetrix.

“High ESR” refers to an above normal ESR as defined in the 2010 ACR/EULAR criteria (Aletaha et al. (2010) Ann. Rheum. Dis. 69:1580-88). According to the 2010 ACR/EULAR criteria, normal / abnormal ESR is based on local laboratory standards. Each local laboratory will employ a cutoff value for abnormal (high) ESR based on that laboratory’s rule for calculating normal maximum ESR. A physician generally orders an ESR test from a local laboratory, and the local laboratory will report normal or high ESR using the rule that laboratory employs to calculate normal ESR. Thus, unless the context dictates otherwise, as used herein “high ESR” is not meant to denote a particular numerical value, as what is considered a normal ESR value will differ between laboratories and assays.

“Rheumatoid factor” or “RF” refers to autoantibodies against the Fc portion of IgG antibodies, which are often present in RA patients. As used herein “RF” includes any RF isotype, e.g., IgG, IgE, IgM and IgA. RF can be assayed using a variety of well-known techniques that are available to determine the presence or absence of a particular antibody, e.g., an ELISA assay, an agglutination test, a nephelometry test, etc. RF levels may be reported by laboratories in a

variety of ways, e.g., IU/ml, units/ml, and titer (using a dilution test to measure how much a blood sample from a patient may be diluted before RF can no longer be detected, e.g., a titer of 1:80 indicates more detectable RF than a titer of 1:20). RF kits are commercially available, e.g., from IBL - America (Immuno-Biological Laboratories).

A patient that is seropositive for RF is referred to herein as “RF+”. Similarly, if a sample from a patient has RF, then that sample is “RF+”. Each local laboratory will employ a cutoff value for normal RF levels based on that laboratory’s rule for calculating normal maximum RF. As suggested by Aletaha et al. (2010) Ann. Rheum. Dis. 69:1580-1588, a patient will be considered RF+ based on the upper limit of normal [ULN] for the respective laboratory test and assay; a patient is RF+ if a value greater than the ULN for the respective laboratory test and assay is determined. Accordingly, unless the context dictates otherwise, as used herein “RF+” is not meant to denote a particular numerical value, as the ULN will differ between laboratories and assays. As a non-limiting example, at the time of testing, Laboratory X gives the normal range of RF in the blood as 14 – 60 units/mL. At the time of testing, Laboratory Y gives the normal range of RF in the blood as ≤ 40 IU/ml. At the time of testing, Laboratory Z gives the normal range of RF in the blood as 1:20 to 1:80 titer. Thus, a patient would be RF+ if Laboratory X returned an RF level of greater than 60 units/ml, if Laboratory Y returned an RF value of greater than 40 IU/ml, or if Laboratory Z returned an RF titer greater than 1:80.

The term “seropositive” is used to mean the presence of a specific substance (e.g., RF) in a patient’s blood serum. The term “serotype” is used to mean that a particular patient is seropositive for a particular serologic antigen, e.g., the HLA-DR4 serologic antigen.

“Anti-citrullinated protein antibody”, “ACPA”, “anti-cyclic citrullinated peptide antibody” and “anti-CCP” refers to autoantibodies that bind citrullinated amino acid residues on proteins, which are found in the joints of in RA patients. Cyclic citrullinated peptides are used in *in vitro* tests (e.g., ELISA assays) to determine the presence of ACPA in a patient’s blood; as a result, an ACPA is also referred to as an “anti-CCP” antibody. ACPA levels can be assayed using a variety of well-known techniques that are available to determine the presence or absence of a particular antibody, e.g., agglutination, ELISA assay, etc. ACPA kits are commercially available, e.g., the DIASTAT® anti-CCP test from Axis-Shield Diagnostics, Ltd. (UK) and AxSYM Anti-CCP® kit from Abbot Diagnostics (Germany).

A patient that is seropositive for ACPA is referred to herein as “ACPA+”. Similarly, if a sample from a patient has ACPA, then that sample is “ACPA+”. Each local laboratory will employ a cutoff value for normal ACPA levels based on that laboratory’s rule for calculating normal maximum ACPA. As suggested by Aletaha et al. (2010) *Ann. Rheum. Dis.* 69:1580-1588, a patient will be considered ACPA+ based on the upper limit of normal [ULN] for the respective laboratory test and assay; a patient is ACPA+ if a value greater than the ULN for the respective laboratory test and assay is determined. Accordingly, unless the context dictates otherwise, as used herein “ACPA+” is not meant to denote a particular numerical value, as the ULN will differ between laboratories and assays. As a non-limiting, at the time of testing, Laboratory A gives the reference range of ACPA in the blood as < 20 EU (arbitrary ELISA units). At the time of testing, Laboratory B gives the reference range of ACPA in the blood as < 5 U/ml. Thus, a patient would be ACPA+ if Laboratory A returned an ACPA value greater than 20 EU or if Laboratory B returned an ACPA value of greater than 5 U/ml.

Select normal / abnormal and reference ranges for ACPA, ESR, RF and CRP may be found, e.g., in Fischbach and Dunning (2009) “A Manual of Laboratory and Diagnostic Tests” (8th Edition) Wolters Kluwer/Lippincott Williams and Williams, which is incorporated by reference herein.

The phrase “high risk RA patient” is used to define a patient that: a) is RF+, ACPA+ or both RF+ and ACPA+; and b) has a high level of CRP, a high ESR, or both a high level of CRP and a high ESR. In some embodiments of the disclosed methods, uses, compositions, kits, etc., the patient is a high risk RA patient.

As used herein, “selecting” and “selected” in reference to a patient is used to mean that a particular patient is specifically chosen from a larger group of patients due to the particular patient having a predetermined criteria, e.g., the patient has the SE, an HLA-DRB1*04 allele or an HLA-DRB1*SE allele. Similarly, “selectively treating a patient having RA” refers to providing treatment to an RA patient that is specifically chosen from a larger group of patients due to the particular patient having a predetermined criteria, e.g., the patient has the SE, an HLA-DRB1*04 allele or an HLA-DRB1*SE allele.

As used herein, “predicting” indicates that the methods described herein provide information to enable a health care provider to determine the likelihood that an individual having RA will respond to or will respond more favorably to treatment with an IL-17 binding molecule.

It does not refer to the ability to predict response with 100% accuracy. Instead, the skilled artisan will understand that it refers to an increased probability.

As used herein, “likelihood” and “likely” is a measurement of how probable an event is to occur. It may be used interchangeably with “probability”. Likelihood refers to a probability that is more than speculation, but less than certainty. Thus, an event is likely if a reasonable person using common sense, training or experience concludes that, given the circumstances, an event is probable. In some embodiments, once likelihood has been ascertained, the patient may be treated (or treatment continued, or treatment proceed with a dosage increase) with the IL-17 binding molecule or the patient may not be treated (or treatment discontinued, or treatment proceed with a lowered dose) with the IL-17 binding molecule.

The term “obtaining” means to procure, e.g., to acquire possession of in any way.

The phrase “increased likelihood” refers to an increase in the probability that an event will occur. For example, the methods herein allow prediction of whether a patient will display an increased likelihood of responding to treatment with an IL-17 binding molecule or an increased likelihood of responding better to treatment with an IL-17 binding molecule in comparison to a RA patient who does not have the SE or an allele in the HLA-DRB1*04 allelic group or the HLA-DRB1*SE allelic group.

The phrase “further increased likelihood” refers to an additional increase over an already increased likelihood. Data disclosed herein suggests an additive effect of HLA-DRB1*04 alleles. Other data disclosed herein suggests an additive effect of HLA-DRB1*SE alleles. Thus, individuals having one HLA-DRB1*04 allele may have an increased likelihood of responding to treatment with an IL-17 binding molecule, while individuals having two HLA-DRB1*04 alleles may have a further (additive) increased likelihood of responding to treatment with an IL-17 binding molecule. Further, individuals having one HLA-DRB1*SE allele may have an increased likelihood of responding to treatment with an IL-17 binding molecule, while individuals having two HLA-DRB1*SE alleles may have a further (additive) increased likelihood of responding to treatment with an IL-17 binding molecule.

The phrase “decreased likelihood” refers to a decrease in the probability that an event will occur. For example, the methods herein allow prediction of whether a patient will display a decreased likelihood of responding to treatment with an IL-17 binding molecule or a decreased likelihood of responding better to treatment with an IL-17 binding molecule in comparison to a

RA patient who has the SE, or an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group.

“HLA” refers to human leukocyte antigen. The HLA is located on chromosome 6p21.31 and covers a region of about 3.6 Mbp depending on the haplotype. HLA molecules are coded by three groups of genes, HLA class I, HLA class II and HLA class III genes. HLA class I proteins are coded by the genes HLA-A, HLA-B, and HLA-C. HLA class II proteins are coded by the genes HLA-DR, HLA-DQ, HLA-DP, HLA-DM, HLA-DOA and HLA-DOB. The HLA class II proteins are part of the complement system. The polymorphic HLA class I genes HLA-A, -B, and -C and class II genes HLA-DR, -DQ and -DP encode various proteins (see, e.g., hla.alleles.org/proteins/class2.html) and various antigens (see, e.g., hla.alleles.org/antigens/recognised_serology.html).

HLA class II molecules consist of two transmembrane polypeptides, the alpha and beta chain. The beta chain is more polymorphic compared to the alpha chain, and HLA typing is generally undertaken on beta chains (e.g., HLA-DRB1 to DRB9). HLA allele naming is made according to the 2010 WHO Nomenclature Committee for Factors of the HLA System (Marsh et al. (2010) *Tissue Antigens* 75:291-455; Marsh et al. (2010) *Bone Marrow Transplantation* 45:846-8). Several digits are used to identify the HLA allele. The particular HLA locus (HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ and HLA-DP) is separated by the symbol * from two numeric digits, which assigns the serologic equivalent of the antigen (this level describes the “type” or “allelic group”). As an example, HLA-DRB1*04 represents an allelic group from the HLA-DRB1 locus. This “two digit” resolution denotes a group of alleles (e.g., a group of alleles from the HLA-DRB1 locus) consisting of various alleles that either encode a similar antigen (e.g., the HLA-DR4 serologic antigen) or that share high sequence homology. This is followed by a colon and another two or three numeric digits, which identifies the specific encoded protein (this level describes the “subtype” or “allelic subtype”). As an example, HLA-DRB1*04:01 is a specific allele within the HLA-DRB1*04 allelic group that encodes a HLA-DR beta chain having a specific amino acid sequence. This “four digit” resolution denotes a particular genomic sequence variation within an allelic group that results in differences in the amino acid sequence of the encoded polypeptide product. Alleles can be further defined using additional colons and numerals that indicate synonymous DNA substitution within the coding region of the allele or that indicate DNA differences in a non-coding region (9 digit level).

“HLA-DRB1*04 allelic group” refers to the allelic group (or type) from the HLA-DRB1 locus consisting of various alleles that either encode the HLA-DR4 serologic antigen or that share high sequence homology.

“HLA-DRB1*04 allele” or “allele in the HLA-DRB1*04 allelic group” refers to an allele within the HLA-DRB1*04 allelic group, e.g., HLA-DRB1*04:01, HLA-DRB1*04:05, etc. IMG/HLA Database (part of the EMBL-EBI database) reference numbers for exemplary HLA-DRB1*04 alleles are shown in **Table 1**, the sequences of which are accessible via www.ebi.ac.uk/imgt/hla/nomenclature/index.html.

Accession # Allele	Accession # Allele	Accession # Allele
HLA00685 DRB1*04:01:01	HLA00699 DRB1*04:13	HLA02146 DRB1*04:53
HLA00686 DRB1*04:01:02	HLA00700 DRB1*04:14	HLA02305 DRB1*04:54
HLA03066 DRB1*04:01:03	HLA00701 DRB1*04:15	HLA02306 DRB1*04:55
HLA04661 DRB1*04:01:04	HLA00702 DRB1*04:16	HLA02314 DRB1*04:56
HLA04663 DRB1*04:01:05	HLA00703 DRB1*04:17:01	HLA02460 DRB1*04:57
HLA04664 DRB1*04:01:06	HLA04408 DRB1*04:17:02	HLA02534 DRB1*04:58
HLA00687 DRB1*04:02	HLA00704 DRB1*04:18	HLA02580 DRB1*04:59
HLA00688 DRB1*04:03:01	HLA00705 DRB1*04:19	HLA02604 DRB1*04:60
HLA01009 DRB1*04:03:02	HLA00706 DRB1*04:20	HLA02705 DRB1*04:61
HLA02717 DRB1*04:03:03	HLA00707 DRB1*04:21	HLA02726 DRB1*04:62
HLA03172 DRB1*04:03:04	HLA00708 DRB1*04:22	HLA02741 DRB1*04:63
HLA04660 DRB1*04:03:05	HLA00709 DRB1*04:23	HLA02804 DRB1*04:64
HLA00689 DRB1*04:04:01	HLA00710 DRB1*04:24	HLA03028 DRB1*04:65
HLA04039 DRB1*04:04:02	HLA00711 DRB1*04:25	HLA03056 DRB1*04:66
HLA04659 DRB1*04:04:03	HLA00712 DRB1*04:26	HLA03060 DRB1*04:67
HLA04662 DRB1*04:04:04	HLA00713 DRB1*04:27	HLA03070 DRB1*04:68
HLA04710 DRB1*04:04:05	HLA00714 DRB1*04:28	HLA03071 DRB1*04:69
HLA00690 DRB1*04:05:01	HLA00715 DRB1*04:29	HLA03073 DRB1*04:70
HLA00691 DRB1*04:05:02	HLA00716 DRB1*04:30	HLA03074 DRB1*04:71
HLA01551 DRB1*04:05:03	HLA00717 DRB1*04:31	HLA03158 DRB1*04:72:01
HLA01605 DRB1*04:05:04	HLA00718 DRB1*04:32	HLA04673 DRB1*04:72:02
HLA03055 DRB1*04:05:05	HLA01088 DRB1*04:33	HLA03167 DRB1*04:73
HLA03375 DRB1*04:05:06	HLA01167 DRB1*04:34	HLA03296 DRB1*04:74
HLA04012 DRB1*04:05:07	HLA01235 DRB1*04:35	HLA03371 DRB1*04:75
HLA04035 DRB1*04:05:08	HLA01242 DRB1*04:36	HLA03372 DRB1*04:76
HLA04654 DRB1*04:05:09	HLA01338 DRB1*04:37	HLA03374 DRB1*04:77
HLA04857 DRB1*04:05:10	HLA01345 DRB1*04:38	HLA03585 DRB1*04:78
HLA00692 DRB1*04:06:01	HLA01458 DRB1*04:39	HLA03993 DRB1*04:79
HLA02172 DRB1*04:06:02	HLA01454 DRB1*04:40	HLA03998 DRB1*04:80
HLA04038 DRB1*04:06:03	HLA01459 DRB1*04:41	HLA04005 DRB1*04:81N
HLA05777 DRB1*04:06:04	HLA01457 DRB1*04:42	HLA04010 DRB1*04:82
HLA00693 DRB1*04:07:01	HLA01499 DRB1*04:43	HLA04036 DRB1*04:83
HLA01453 DRB1*04:07:02	HLA01601 DRB1*04:44	HLA04040 DRB1*04:84
HLA01706 DRB1*04:07:03	HLA01695 DRB1*04:45	HLA04349 DRB1*04:85
HLA04658 DRB1*04:07:04	HLA01746 DRB1*04:46	HLA04382 DRB1*04:86
HLA00694 DRB1*04:08:01	HLA01780 DRB1*04:47	HLA04383 DRB1*04:87

HLA04008 DRB1*04:08:02	HLA01793 DRB1*04:48	HLA04384 DRB1*04:88
HLA00695 DRB1*04:09	HLA01810 DRB1*04:49	HLA04672 DRB1*04:89
HLA00696 DRB1*04:10	HLA01817 DRB1*04:50	HLA05128 DRB1*04:90
HLA00697 DRB1*04:11	HLA02039 DRB1*04:51	HLA05146 DRB1*04:91
HLA00698 DRB1*04:12	HLA02054 DRB1*04:52	HLA05868 DRB1*04:92

Table 1: IMG/HLA Database reference numbers for HLA-DRB1*04 alleles. New HLA-DRB1*04 alleles can be discovered and this list is not exhaustive.

The use of the phrase “the at least one allele”, in reference to a prior recitation of “allele in the HLA-DRB1*04 allelic group” refers to an HLA-DRB1*04 allele. These sequences are incorporated by reference herein in their entirety.

“Product of an HLA-DRB1*04 allele” includes nucleic acid products of an HLA-DRB1*04 allele, e.g., mRNA, micro RNAs, fragments of RNAs etc. and polypeptide products of an HLA-DRB1*04 allele. “Polypeptide product of an HLA-DRB1*04 allele” refers to a polypeptide encoded by an HLA-DRB1*04 allele, a fragment of a polypeptide encoded by an HLA-DRB1*04 allele and the HLA-DR4 serologic antigen. “Nucleic acid product of an HLA-DRB1*04 allele” refers to any RNA products of the HLA-DRB1*04 allele and fragments thereof.

“HLA-DR4 serotype” refers to the serotype of a patient expressing a polypeptide product of an HLA-DRB1*04 allele (e.g., a HLA-DR4 serologic antigen).

The “shared epitope” or “SE” is an epitope of amino acid sequence R/Q⁷⁰ K/R R A A⁷⁴ (SEQ ID NO:18) found at positions 70-74 in the third hypervariable region of the DRB1 chain. The shared epitope is currently understood to be present in the following alleles: HLA-DRB1*01:01, HLA-DRB1*01:02 and HLA-DRB1*01:04 (referred to as the HLA-DRB1*01 SE allelic group); HLA-DRB1*04:01 (previously referred to as type Dw4), HLA-DRB1*04:04, HLA-DRB1*04:05, HLA-DRB1*04:08, HLA-DRB1*04:09, HLA-DRB1*04:10, HLA-DRB1*04:13, HLA-DRB1*04:16, HLA-DRB1*04:19, HLA-DRB1*04:21 (referred to as the HLA-DRB1*04 SE allelic group); HLA-DRB1*10:01; HLA-DRB1*13:03; HLA-DRB1*14:02 and HLA-DRB1*14:06 (referred to as the HLA-DRB1*14 SE allelic group). Gorman and Criswell (2002) Genetics 28:59-77. A classification system for RA risk conferred by HLA-DRB1 alleles, including alleles encoding polypeptide products having the SE, may be found in J. Imboden (2009) Annu. Rev. Pathol. Mech. Dis. 4:417-34, which is incorporated by reference herein in its entirety. Additional information on the SE may be found in Holoshitz (2010) Current Opinion in Rheumatology 22:293-298.

As used herein, “HLA-DRB1*SE allelic group” refers to an allelic group (or type) from the HLA-DRB1 locus consisting of the following alleles: HLA-DRB1*01:01, HLA-DRB1*01:02, HLA-DRB1*04:01, HLA-DRB1*04:04, HLA-DRB1*04:05, HLA-DRB1*04:08, HLA-DRB1*10:01, and HLA-DRB1*14:02. Notably, some alleles in HLA-DRB1*SE allelic group are also in the HLA-DRB1*04 allelic group. As such, in some cases, detecting an allele in the HLA-DRB1*SE allelic group can also result in detection of an allele in the HLA-DRB1*04 allelic group (and vice versa). IMG/HLA Database reference numbers for exemplary HLA-DRB1*SE alleles are accessible via www.ebi.ac.uk/imgt/hla/nomenclature/index.html. “HLA-DRB1*SE allele” or “allele in the HLA-DRB1*SE allelic group” refers to an allele within the HLA-DRB1*SE allelic group, e.g., HLA-DRB1*01:01, HLA-DRB1*01:02. The use of the phrase “the at least one allele”, in reference to a prior recitation of “allele in the HLA-DRB1*SE allelic group” refers to an HLA-DRB1*SE allele.

“Product of the HLA-DRB1*SE allele” includes nucleic acid products of an HLA-DRB1*SE allele, e.g., mRNA, micro RNAs, fragments of RNAs, etc. and polypeptide products of an HLA-DRB1*SE allele. “Polypeptide product of an HLA-DRB1*SE allele” refers to a polypeptide encoded by an HLA-DRB1*SE allele, a fragment of a polypeptide encoded by an HLA-DRB1*SE allele and the SE. “Nucleic acid product of an HLA-DRB1*SE allele” refers to any RNA products of the HLA-DRB1*SE allele and fragments thereof.

“HLA-DRSE serotype” refers to the serotype of a patient expressing a polypeptide product of an HLA-DRB1*SE allele.

An “equivalent genetic marker” of an allele of interest (e.g., an HLA-DRB1*04 allele or an HLA-DRB1*SE allele) refers to a genetic marker that is correlated to the allele of interest, e.g., it displays linkage disequilibrium or is in genetic linkage with the allele of interest. Equivalent genetic markers may be used to determine if a patient has a SE, an allele in the HLA-DRB1*04 allelic group, and/or an allele in the HLA-DRB1*SE allelic group.

The term “probe” refers to any substance useful for specifically detecting another substance, e.g., a substance related to the SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group. A probe can be an oligonucleotide or conjugated oligonucleotide that specifically hybridizes to a particular region within an HLA-DRB1*04 allele or an HLA-DRB1*SE allele. The conjugated oligonucleotide refers to an oligonucleotide covalently bound to chromophore or molecules containing a ligand (e.g., an antigen), which is

highly specific to a receptor molecule (e.g., an antibody specific to the antigen). The probe can also be a PCR primer, together with another primer, for amplifying a particular region within an HLA-DRB1*04 allele or an HLA-DRB1*SE allele. Further, the probe can be an antibody that specifically recognizes an HLA-DRB1*04 allele or an HLA-DRB1*SE allele or a polypeptide product or serologic antigen of an HLA-DRB1*04 allele or an HLA-DRB1*SE allele. Further, the probe can be any substance capable of detecting an equivalent genetic marker of an HLA-DRB1*04 allele or an HLA-DRB1*SE allele.

As used herein, “genomic sequence” refers to a DNA sequence present in a genome, and includes a region within an allele, an allele itself, or a larger DNA sequence of a chromosome containing an allele of interest.

The term “biological sample” as used herein refers to a sample from a patient, which may be used for the purpose of identification, diagnosis, prediction, or monitoring. Preferred test samples include synovial fluid, blood, blood-derived product (such as buffy coat, serum, and plasma), lymph, urine, tear, saliva, cerebrospinal fluid, buccal swabs, sputum, or tissue samples. In addition, one of skill in the art would realize that some test samples would be more readily analyzed following a fractionation or purification procedure, for example, isolation of DNA from whole blood.

An “oligonucleotide” refers to a short sequence of nucleotides, e.g., 2-100 bases.

The term “capable” is used to mean that ability to achieve a given result, e.g., a probe that is capable of detecting the presence of a particular substance means that the probe is able to detect the particular substance.

The phrases “has been previously treated for RA” and “had a previous RA treatment” and the like are used to mean a patient that has previously undergone RA therapy, e.g., using an anti-rheumatic agent, e.g., the patient is a failure, an inadequate responder, or intolerant to a previous RA therapy, anti-rheumatic agent or treatment regimen. Such patients include those previously treated with MTX, DMARDs, and/or biologics, such as TNF alpha antagonists, etc. The phrase “has not been previously treated for RA” is used to mean a patient that has not previously undergone RA treatment using an anti-rheumatic agent, i.e., the patient is “naïve”.

The term “failure” to a previous RA therapy refers to: (1) a patient who has no meaningful clinical benefit (primary lack of efficacy); (2) a patient who has a measurable and meaningful response, but for whom response could be better, e.g., low RA disease activity or RA remission

was not achieved (also termed “inadequate response”); (3) a patient who, after an initial good response, worsens (secondary loss of efficacy); and (4) a patient who has a good response but discontinues because of a side effect (also termed “intolerance”). Patients who show TNF inadequate response (TNF-IR) or intolerance to TNF would be considered TNF failures. Patients who show methotrexate inadequate response (MTX-IR) or intolerance to MTX would be considered MTX failures. Patients who show DMARD inadequate response (DMARD-IR) or intolerance to DMARDs would be considered DMARD failures.

The phrase “therapeutic regimen” means the pattern of treatment of an illness, e.g., the pattern of dosing used during the treatment of RA. A therapeutic regimen may include an induction regimen and a maintenance regimen.

The phrase “induction regimen” or “induction period” refers to a treatment regimen (or the portion of a treatment regimen) that is used for the initial treatment of a disease. In some embodiments, the disclosed methods, uses, kits, processes and regimens (e.g., methods of treating an inflammatory arthritis, e.g., RA, such as a high risk RA patient) employ an induction regimen. The general goal of an induction regimen is to provide a high level of drug to a patient during the initial period of a treatment regimen. An induction regimen may employ (in part or in whole) administration of a greater dose of the drug than a physician would employ during a maintenance regimen, administering a drug more frequently than a physician would administer the drug during a maintenance regimen, or both. In some embodiments of the disclosed methods, uses, kits, processes and regimens the induction dose may be delivered during an induction regimen as a single high dose infusion (e.g., about 30 mg/kg). Alternatively, an induction dose may be delivered as several (e.g., two or three) infusions (e.g., about 10 mg/kg). Alternatively, an induction dose may be delivered as several subcutaneous injections (e.g., about 75-300 mg). Delivery of drug during an induction regimen may be via a subcutaneous (s.c.) route, e.g., delivery of dosages of about 75 mg - about 300 mg s.c. (e.g., about 75 mg s.c., about 150 mg s.c., about 300 mg s.c.), or via an intravenous (i.v.) route, e.g., delivery of dosages of about 1 mg/kg - about 30 mg/kg i.v. (e.g., about 1 mg/kg, about 3 mg/kg, about 10 mg/kg, about 30 mg/kg) or any other route of administration (e.g., intramuscular, i.m.). In some embodiments of the disclosed methods, compositions, kits, uses and regimens the IL-17 antagonist (e.g., secukinumab) is delivered by i.v. administration during at least a portion of the induction regimen. In some embodiments, the induction regimen comprises administering a dose of about

1 mg/kg – about 30 mg/kg, about 1 mg/kg – about 10 mg/kg, preferably about 10 mg/kg of the IL-17 antagonist (e.g., secukinumab). In further embodiments, the induction doses are delivered weekly, bi-weekly, every other week, or monthly, preferably every other week. In further embodiments, the induction regimen employs 1 – 10 doses of the IL-17 antagonist (e.g., secukinumab), preferably three doses of the IL-17 antagonist (e.g., secukinumab).

The phrase “maintenance regimen” or “maintenance period” refers to a treatment regimen (or the portion of a treatment regimen) that is used for the maintenance of a patient during treatment of an illness, e.g., to keep the patient in remission for long periods of time (months or years). In some embodiments, the disclosed methods, uses and regimens (e.g., methods of treating an inflammatory arthritis, e.g., RA, such as a high risk RA patient) employ a maintenance regimen. A maintenance regimen may employ continuous therapy (e.g., administering a drug at a regular intervals, e.g., weekly, monthly, yearly, etc.) or intermittent therapy (e.g., interrupted treatment, intermittent treatment, treatment at relapse, or treatment upon achievement of a particular predetermined criteria [e.g., pain, disease manifestation, etc.]). Delivery of drug during a maintenance regimen may be via a subcutaneous route, e.g., delivery of dosages of about 75 mg - about 300 mg s.c. (e.g., about 75 mg s.c., about 150 mg s.c., about 300 mg s.c.), or via an intravenous route, e.g., delivery of dosages of about about 1 mg/kg - about 30 mg/kg i.v. (e.g., about 1 mg/kg, about 3 mg/kg, about 10 mg/kg, about 30 mg/kg), or any other route of administration (e.g., intramuscular, i.m.). In some embodiments of the disclosed methods, uses and regimens, the IL-17 antagonist (e.g., secukinumab) is delivered by s.c. administration during the maintenance regimen. In some embodiments, the maintenance regimen comprises administering a dose of about 75 mg – about 300 mg, about 75 mg – about 150 mg, preferably about 75 mg or about 150 mg of the IL-17 antagonist (e.g., secukinumab). In some embodiments, the maintenance regimen comprises administering a dose of the IL-17 antagonist (e.g., secukinumab) on a monthly basis.

The phrase “means for administering” is used to indicate any available implement for systemically administering a drug to a patient, including, but not limited to, a pre-filled syringe, a vial and syringe, an injection pen, an autoinjector, an i.v. drip and bag, a pump, etc. With such items, a patient may self-administer the drug (i.e., administer the drug on their own behalf) or a physician may administer the drug.

The phrase “specifically hybridizes” is used to refer to specific binding under stringent hybridization conditions. 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 “a region of a nucleic acid” is used to indicate a smaller sequence within a larger sequence of nucleic acids. For example, a gene is a region of a chromosome, an exon is a region of a gene, etc.

Various aspects of the disclosure are described in further detail in the following subsections. All patents, patent applications, references and other publications are incorporated by reference herein in their entirety.

IL-17 Antagonists and Pharmaceutical Compositions

The various disclosed pharmaceutical compositions, regimens, processes, uses, methods and kits utilize an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof).

In one embodiment, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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).

In one embodiment, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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-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).

In one embodiment, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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).

In one embodiment, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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 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; 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 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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: 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 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; 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 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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 secukinumab monoclonal antibody, based on the Kabat definition and as determined by the X-ray analysis and using the approach of Chothia and coworkers, is provided in **Table 2**, below.

Light-Chain		
CDR1'	Kabat	R-A-S-Q-S-V-S-S-S-Y-L-A (SEQ ID NO:4)
	Chothia	R-A-S-Q-S-V-S-S-S-Y-L-A (SEQ ID NO:4)
CDR2'	Kabat	G-A-S-S-R-A-T (SEQ ID NO:5)
	Chothia	G-A-S-S-R-A-T (SEQ ID NO:5)
CDR2'	Kabat	Q-Q-Y-G-S-S-P-C-T (SEQ ID NO:6)
	Chothia	Q-Q-Y-G-S-S-P-C-T (SEQ ID NO:6)
Heavy-Chain		
CDR1	Kabat	N-Y-W-M-N (SEQ ID NO:1)
CDR1-x	Chothia	G-F-T-F-S-N -Y-W-M-N (SEQ ID NO:11)
CDR2	Kabat	A-I-N-Q-D-G-S-E-K-Y-Y-V-G-S-V-K-G (SEQ ID NO:2)
CDR2-x	Chothia	A-I-N-Q-D-G-S-E-K-Y-Y (SEQ ID NO:12)
CDR3	Kabat	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	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 2: Amino acid sequences of the hypervariable regions of the secukinumab 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.

In preferred embodiments, the variable domains of both heavy and light chains are of human origin, for instance those of the secukinumab 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, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) comprises the variable light domain of SEQ ID NO:10. In other embodiments, the IL-17 antagonist comprises the variable heavy domain of SEQ ID NO:8. In other embodiments, the IL-17 antagonist comprises the variable light domain of SEQ ID NO:10 and the variable heavy domain of SEQ ID NO:8. In some embodiments, the IL-17 antagonist comprises the three CDRs of SEQ ID NO:10. In other

embodiments, the IL-17 antagonist comprises the three CDRs of SEQ ID NO:8. In other embodiments, the IL-17 antagonist comprises the three CDRs of SEQ ID NO:10 and the three CDRs of SEQ ID NO:8. CDRs of SEQ ID NO:8 and SEQ ID NO:10, according to both the Chothia and Kabat definition, may be found in **Table 2**.

In some embodiments, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) comprises the light domain of SEQ ID NO:15. In other embodiments, the IL-17 antagonist comprises the heavy domain of SEQ ID NO:17. In other embodiments, the IL-17 antagonist comprises the light domain of SEQ ID NO:15 and the heavy domain of SEQ ID NO:17. In some embodiments, the IL-17 antagonist comprises the three CDRs of SEQ ID NO:15. In other embodiments, the IL-17 antagonist comprises the three CDRs of SEQ ID NO:17. In other embodiments, the IL-17 antagonist comprises the three CDRs of SEQ ID NO:15 and the three CDRs of SEQ ID NO:17. CDRs of SEQ ID NO:15 and SEQ ID NO:17, according to both the Chothia and Kabat definition, may be found in **Table 2**.

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 secukinumab 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 secukinumab 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, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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 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 CDR1', CDR2', and CDR3' 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, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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, 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', 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.

Alternatively, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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 antagonist 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 being measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Similarly, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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 antagonist 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 being measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Similarly, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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 antagonist 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 being measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Alternatively, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) may comprise both heavy (V_H) and light chain (V_L) variable domains and said IL-17 binding molecule having 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 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'_{1i} 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'_{2i} 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'_{3i} 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 IL-17 antagonist 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 being measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts.

Alternatively, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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 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'_{1i} 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'_{2i} 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'_{3i} 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 IL-17 antagonist 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 being 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 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 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 derivative 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, the IL-17 binding molecules disclosed herein 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 antagonists of the disclosure.

The disclosure also includes IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) 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 antagonists. 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').

The disclosure also includes IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) that have binding specificity for human IL-17, in particular IL-17 antibodies capable of inhibiting the binding of IL-17 to its receptor and IL-17 antibodies 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 being measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts).

In some embodiments, the IL-17 antagonist, e.g., IL-17 antibody, e.g., secukinumab, binds to an epitope of mature human IL-17 comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129. In some embodiments, the IL-17 antibody, e.g., secukinumab, binds to an epitope of mature human IL-17 comprising Tyr43, Tyr44, Arg46, Ala79, Asp80. In some embodiments, the IL-17 antibody, e.g., secukinumab, binds to an epitope of an IL-17 homodimer having two mature human IL-17 chains, said epitope comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129 on one chain and Tyr43, Tyr44, Arg46, Ala79, Asp80 on the other chain. The residue numbering scheme used to define these epitopes is based on residue one being the first amino acid of the mature protein (ie., IL-17A lacking the 23 amino acid N-terminal signal peptide and beginning with Glycine). The sequence for immature IL-17A is set forth in the Swiss-Prot entry Q16552. In some embodiments, the IL-17 antibody has a K_D of about 100-200 pM. In some embodiments, the IL-17 antibody has an IC_{50} of about 0.4 nM for *in vitro* neutralization of the biological activity of about 0.67 nM human IL-17A. In some embodiments, the absolute bioavailability of subcutaneously (s.c.) administered IL-17 antibody has a range of about 60 – about 80%, e.g., about 76%. In some embodiments, the IL-17 antagonist, e.g., an IL-17 binding molecule (e.g., an IL-17 antibody, such as secukinumab) or an IL-17 receptor binding molecule (e.g., an IL-17 receptor antibody) has an elimination half-life of about 4 weeks (e.g., about 23 to about 30 days, e.g., about 30 days). In some embodiments, the IL-17 antagonist, e.g., an IL-17 binding molecule (e.g., an IL-17 antibody, such as secukinumab) or an IL-17 receptor binding molecule (e.g., an IL-17 receptor antibody) has a T_{max} of about 7-8 days.

Particularly preferred IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof) for use in the disclosed methods, uses, kits, etc. are human antibodies, especially secukinumab as described in Examples 1 and 2 of WO 2006/013107. Secukinumab is a recombinant 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. Secukinumab (see, e.g., WO2006/013107 and WO2007/117749) has a very high affinity for IL-17, i.e., a K_D of about 100-200 pM and an IC_{50} for *in vitro* neutralization of the biological activity of about 0.67 nM human IL-17A of about 0.4 nM. Thus, secukinumab inhibits antigen

at a molar ratio of about 1:1. This high binding affinity makes the secukinumab antibody particularly suitable for therapeutic applications. Furthermore, it has been determined that secukinumab has a very long half life, i.e., about 4 weeks, which allows for prolonged periods between administration, an exceptional property when treating chronic life-long disorders, such as rheumatoid arthritis (RA).

Predictive Methods, Diagnostic Methods and Methods of Producing a Transmittable Form of Information

The disclosed methods are useful for the treatment, prevention, or amelioration of inflammatory arthritis (e.g., rheumatoid arthritis (RA), spondyloarthropathy, ankylosing spondylitis, and psoriatic arthritis).

A biological sample from the patient may be assayed for a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group by any conventional means, e.g., Western blot, Northern blot, ELISA, etc. The invention is not limited by the types of assays used to assess the presence of a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group in a biological sample from a patient. Indeed, any well-known assay that can be employed to determine the genotypic status of the patient can be employed for the purposes of the present invention.

The invention is also not limited by the source of the biological sample, as numerous biological samples may be used to identify the presence or absence of a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group in the patient, e.g., blood, synovial fluid, buffy coat, serum, plasma, lymph, urine, tear, saliva, cerebrospinal fluid, buccal swabs, sputum, or tissue. The invention is also not limited by the source within the biological sample used to identify the presence or absence of a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group. It will be recognized that one may assay genomic DNA obtained from a biological sample to detect a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group, or one may assay products of an HLA-DRB*04 allele and/or an HLA-DRB*SE allele, e.g., nucleic acid products (e.g., mRNA, micro RNAs, etc.) and polypeptide products (e.g., serologic antigens) obtained from a biological sample to detect a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group. Furthermore, a SE, an allele in the HLA-

DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group can also be determined by detecting an equivalent genetic marker of an HLA-DRB*04 allele or an HLA-DRB*SE allele, which can be, e.g., a SNP (single nucleotide polymorphism), a microsatellite marker, another HLA allele (e.g., an HLA-DQB1 allele) or other kinds of genetic polymorphisms. For example, the presence of a genetic marker on the same haplotype as an HLA-DRB1*04 allele, rather than an HLA-DRB1*04 allele *per se*, may be indicative of a patient's likelihood for responding to treatment with an IL-17 binding molecule. A discussion of recombination and linkage disequilibrium within the HLA class II region is provided in Begovich et al. (1992) J. Immunology 148:249-58. Consequently, the presence of equivalent genetic markers may also be used in the disclosed methods. Preferably, the useful equivalent genetic markers are about 200 kb or less from the HLA allele of interest. More preferably, the equivalent genetic markers are 100 kb or less from the HLA allele of interest. Exemplary equivalent genetic markers of the HLA haplotypes include SNPs tagging the haplotype, or an allele encoded by a gene from this haplotype (e.g., allele DQB1*03:02 coding for the DQ8 antigen, part of the DR4-DQ8 haplotype).

Numerous methods and devices are well known to the skilled artisan to identify the presence or absence of a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group. For example, the presence or absence of an HLA-DRB1*04 and/or HLA-DRB1*SE allele can be determined by direct detection of the alleles (e.g., by marker) or by detection of particular regions therein. DNA for allele detection can be prepared from a biological sample by methods well known in the art, e.g., PUREGENE DNA® purification system from Gentra Systems (Qiagen, CA). Detection of a genomic sequence may include examining the nucleotide(s) located at either the sense or the anti-sense strand within that region.

The presence or absence of a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group in a patient may be detected from genomic DNA obtained from PCR using sequence-specific probes, e.g., hydrolysis probes from Taqman, Beacons, Scorpions; or hybridization probes that detect a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group. For the detection, sequence specific probes are designed such that they specifically hybridize to the genomic DNA for the

HLA alleles of interest. These probes may be labeled for direct detection or contacted by a second, detectable molecule that specifically binds to the probe. The PCR products also can be detected by DNA-binding agents. Said PCR products can then be subsequently sequenced by any DNA sequencing method available in the art.

Alternatively the presence or absence of HLA alleles can be detected by sequencing using any sequencing methods such as, but not limited to, Sanger-based sequencing, pyrosequencing or next generation sequencing (Shendure J. and Ji, H., *Nature Biotechnology* (1998), Vol. 26, Nr 10, pages 1135-1145)

In some embodiments, the presence or absence of a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group in a patient is detected using a hybridization assay. In a hybridization assay, the presence or absence of the genetic marker is determined based on the ability of the nucleic acid from the sample to hybridize to a complementary nucleic acid molecule, e.g., an oligonucleotide probe. A variety of hybridization assays are available. In some, hybridization of a probe to the sequence of interest is detected directly by visualizing a bound probe, e.g., a Northern or Southern assay. In these assays, DNA (Southern) or RNA (Northern) is isolated. The DNA or RNA is then cleaved with a series of restriction enzymes that cleave infrequently in the genome and not near any of the markers being assayed. The DNA or RNA is then separated, e.g., on an agarose gel, and transferred to a membrane. A labeled probe or probes, e.g., by incorporating a radionucleotide or binding agent (e.g., SYBR® Green), is allowed to contact the membrane under low-, medium- or high-stringency conditions. Unbound probe is removed and the presence of binding is detected by visualizing the labeled probe.

Various methods of assaying, detecting, measuring, identifying and/or determining HLA alleles and allelic regions are known in the art. HLA-typing can be undertaken at low, intermediate or high resolution. Low resolution HLA typing refers to alleles which are reported at the two-digit level (e.g., HLA-DRB1*04). Intermediate resolution HLA-typing occurs when a level of ambiguity exists, even though a patient has been typed at the four digit level. For example, one may know only a list of possibilities, i.e., HLA-DRB1*03:01- HLA-DRB1*30:01 or HLA-DRB1*03:20- HLA-DRB1*30:01 or HLA-DRB1*03:26- HLA-DRB1*30:01. Such intermediate resolution types may result from sequence-specific PCR (SSP) based typing where testing with the initial set of PCR primers will yield a list of possible genotypes that a particular

person might have (which may require further testing with additional combinations of allele-specific primers and/or cloning and sequencing of clones before an unambiguous type is achieved). However, depending on the clinical and/or research purpose of the HLA typing, additional laboratory testing can achieve high-level (i.e., four-digit) resolution.

Low resolution HLA typing can be achieved by antibody-based serological tests. Higher resolution is achievable with molecular (DNA-based methods). Such methods of HLA-typing include, e.g., DNA amplification techniques such as PCR and variants thereof, direct sequencing, Sequence Specific Oligonucleotide (SSO) hybridization coupled with the Luminex xMAP® technology, Sequence Specific Primer (SSP) typing, Sequence Based Typing (SBT).

Sequence-Specific Oligonucleotide (SSO) typing uses PCR target amplification, hybridization of PCR products to a panel of immobilized sequence-specific oligonucleotides on the beads, detection of probe-bound amplified product by color formation followed by data analysis. Those skilled in the art would understand that the described Sequence-Specific Oligonucleotide (SSO) hybridization may be performed using various commercially available kits, such as those provided by One Lambda, Inc. (Canoga Park, CA) or Lifecodes HLA Typing Kits (Tepnel Life Sciences Corp.) coupled with Luminex® technology (Luminex, Corporation, TX). LABType® SSO is a reverse SSO (rSSO) DNA typing solution that uses sequence-specific oligonucleotide (SSO) probes and color-coded microspheres to identify HLA alleles. The target DNA is amplified by polymerase chain reactions (PCR) and then hybridized with the bead probe array. The assay takes place in a single well of a 96-well PCR plate; thus, 96 samples can be processed at one time.

Sequence Specific Primers (SSP) typing is a PCR based technique which uses sequence specific primers for DNA based HLA typing. The SSP method is based on the principle that only primers with completely matched sequences to the target sequences result in amplified products under controlled PCR conditions. Allele sequence-specific primer pairs are designed to selectively amplify target sequences which are specific to a single allele or group of alleles. PCR products can be visualized on agarose gel. Control primer pairs that matches non-allelic sequences present in all samples act as an internal PCR control to verify the efficiency of the PCR amplification. Those skilled in the art would understand that low, medium and high resolution genotyping with the described sequence-specific primer typing may be performed

using various commercially available kits, such as the Olerup SSPT[™] kits (Olerup, PA) or (Invitrogen) or Allset and [™]Gold DQA1 Low resolution SSP (Invitrogen).

Sequence Based Typing (SBT) is based on PCR target amplification, followed by sequencing of the PCR products and data analysis.

Messenger RNA (mRNA) levels can also be used as a predictive marker to determine if an individual is likely to be responsive to treatment with an IL-17 binding molecule. Levels of mRNA are measured using any of a number of techniques known to those skilled in the art including, but not limited to Northern blot analysis, nuclease protection assays (NPA), in situ hybridization, reverse transcription-polymerase chain reaction (RT-PCR), RT-PCR ELISA, TaqMan-based quantitative RT-PCR (probe-based quantitative RT-PCR) and SYBR green-based quantitative RT-PCR.

In one example, detection of mRNA levels involves contacting the isolated mRNA with an oligonucleotide that can hybridize to mRNA encoded by an HLA-DRB1*04 and/or HLA-DRB1*SE allele. The nucleic acid probe can typically be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, or 100 nucleotides in length and sufficient to specifically hybridize under stringent conditions to the mRNA. Hybridization of an mRNA with the probe indicates that the marker in question is being expressed.

In one format, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose.

In another example, the level of the mRNA can be determined by reverse transcription-polymerase chain reaction (RT-PCR), RT-PCR ELISA, TaqMan-based quantitative RT-PCR (probe-based quantitative RT-PCR) and SYBR green-based quantitative RT-PCR. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. Amplification primers are defined as being a pair of nucleic acid molecules that can anneal to 5' or 3' regions of a gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such primers permit the amplification of a nucleic acid molecule comprising the nucleotide sequence flanked

by the primers. PCR products can be detected by any suitable method including, but not limited to, gel electrophoresis and staining with a DNA-specific stain or hybridization to a labeled probe.

In one embodiment, the presence of a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group in a patient is determined by measuring RNA levels using, e.g., a PCR-based assay or reverse-transcriptase PCR (RT-PCR). In yet another aspect, the quantitative RT-PCR with standardized mixtures of competitive templates can be utilized.

One of skill in the art would recognize that the analysis of an HLA-DRB*04 and/or HLA-DRB*SE allele may be carried out separately or simultaneously while analyzing other genetic sequences. In another aspect of the present disclosure, an array is provided to which probes that correspond in sequence to gene products, e.g., cDNAs, mRNAs, cRNAs, polypeptides and fragments thereof, can be specifically hybridized or bound at a known position.

In some embodiments, the presence or absence of a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group in a patient is determined by measuring polypeptide products of the HLA-DRB*04 and/or HLA-DRB*SE alleles. Detection of polypeptide products of HLA-DRB1*04 and/or HLA-DRB1*SE alleles (HLA-DR4 and HLA-DRSE serologic antigens) can be performed using any known method in the art including, but not limited, to immunocytochemical staining, ELISA, flow cytometry, Western blot, spectrophotometry, HPLC, and mass spectrometry. In some embodiments, serologic-based HLA typing uses antigen-specific sera to determine a patient's HLA type.

One method for detecting polypeptide products of HLA-DRB1*04 and/or HLA-DRB1*SE alleles in a sample is by means of a probe that is a binding protein capable of interacting specifically with a marker protein. Preferably, labeled antibodies, binding portions thereof, or other binding partners can be used. The antibodies can be monoclonal or polyclonal in origin, or may be biosynthetically produced. The binding partners may also be naturally occurring molecules or synthetically produced. The amount of complexed proteins is determined using standard protein detection methodologies described in the art. A detailed review of immunological assay design, theory and protocols can be found in numerous texts in the art, including Practical Immunology, Butt, W. R., ed., Marcel Dekker, New York, 1984.

A variety of assays are available for detecting proteins with labeled antibodies. Direct labels include fluorescent or luminescent tags, metals, dyes, radionucleides, and the like,

attached to the antibody. Indirect labels include various enzymes well known in the art, such as alkaline phosphatase, hydrogen peroxidase and the like. In a one-step assay, polypeptide products of HLA-DRB1*04 and/or HLA-DRB1*SE alleles, if present, are immobilized and incubated with a labeled antibody. The labeled antibody binds to the immobilized target molecule. After washing to remove unbound molecules, the sample is assayed for the presence of the label.

The use of immobilized antibodies specific for the proteins or polypeptides is also contemplated by the present disclosure. The antibodies can be immobilized onto a variety of solid supports, such as magnetic or chromatographic matrix particles, the surface of an assay plate (such as microtiter wells), pieces of a solid substrate material (such as plastic, nylon, paper), and the like. An assay strip can be prepared by coating the antibody or a plurality of antibodies in an array on solid support. This strip can then be dipped into the test sample and then processed quickly through washes and detection steps to generate a measurable signal, such as a colored spot.

In a two-step assay, immobilized polypeptide products of HLA-DRB1*04 and/or HLA-DRB1*SE alleles may be incubated with an unlabeled antibody. The unlabeled antibody complex, if present, is then bound to a second, labeled antibody that is specific for the unlabeled antibody. The sample is washed and assayed for the presence of the label.

The choice of marker used to label the antibodies will vary depending upon the application. However, the choice of the marker is readily determinable to one skilled in the art.

The antibodies may be labeled with a radioactive atom, an enzyme, a chromophoric or fluorescent moiety, or a colorimetric tag. The choice of tagging label also will depend on the detection limitations desired. Enzyme assays (ELISAs) typically allow detection of a colored product formed by interaction of the enzyme-tagged complex with an enzyme substrate. Some examples of radioactive atoms include ^{32}P , ^{125}I , ^3H , and ^{14}P . Some examples of enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, and glucose-6-phosphate dehydrogenase. Some examples of chromophoric moieties include fluorescein and rhodamine. The antibodies may be conjugated to these labels by methods known in the art. For example, enzymes and chromophoric molecules may be conjugated to the antibodies by means of coupling agents, such as dialdehydes, carbodiimides, dimaleimides, and the like. Alternatively,

conjugation may occur through a ligand-receptor pair. Some suitable ligand-receptor pairs include, for example, biotin-avidin or -streptavidin, and antibody-antigen.

In one aspect, the present disclosure contemplates the use of a sandwich technique for detecting polypeptide products of HLA-DRB1*04 and/or HLA-DRB1*SE alleles in biological samples. The technique requires two antibodies capable of binding the protein of interest: e.g., one immobilized onto a solid support and one free in solution, but labeled with some easily detectable chemical compound. Examples of chemical labels that may be used for the second antibody include but are not limited to radioisotopes, fluorescent compounds, and enzymes or other molecules which generate colored or electrochemically active products when exposed to a reactant or enzyme substrate. When samples containing polypeptide products of HLA-DRB1*04 and/or HLA-DRB1*SE alleles are placed in this system, the polypeptide products binds to both the immobilized antibody and the labeled antibody. The result is a "sandwich" immune complex on the support's surface. The complexed protein is detected by washing away nonbound sample components and excess labeled antibody, and measuring the amount of labeled antibody complexed to protein on the support's surface. The sandwich immunoassay is highly specific and very sensitive, provided that labels with good limits of detection are used.

Preferably, the presence of polypeptide products of HLA-DRB1*04 and/or HLA-DRB1*SE alleles in a sample is detected by radioimmunoassays or enzyme-linked immunoassays, competitive binding enzyme-linked immunoassays, dot blot, Western blot, chromatography, preferably high performance liquid chromatography (HPLC), or other assays known in the art. Specific immunological binding of the antibody to the protein or polypeptide can be detected directly or indirectly.

Dot blotting is routinely practiced by the skilled artisan to detect a desired protein using an antibody as a probe (Promega Protocols and Applications Guide, Second Edition, 1991, Page 263, Promega Corporation). Samples are applied to a membrane using a dot blot apparatus. A labeled probe is incubated with the membrane, and the presence of the protein is detected.

Western blot analysis is well known to the skilled artisan (Sambrook et al., Molecular Cloning, A Laboratory Manual, 1989, Vol. 3, Chapter 18, Cold Spring Harbor Laboratory). In Western blot, the sample is separated by SDS-PAGE. The gel is transferred to a membrane. The membrane is incubated with labeled antibody for detection of the desired protein.

Cellular typing may also be used for HLA-typing. A representative cellular assay is the mixed lymphocyte culture (MLC), which is used to determine the HLA class II types. The cellular assay is more sensitive in detecting HLA differences than serotyping. This is because minor differences unrecognized by alloantisera can stimulate T cells. This typing is designated as Dw types. Serotyped DR4 has been cellularly defined as DR4 Dw4, Dw10, Dw13, Dw14, Dw15.

A review of various methods to perform HLA typing may be found as Howell et al. (2009) J Clin Pathol 2010 63: 387-390. Kits for HLA typing are available from, e.g, Biotest AG, Dreieich, German; Qiagen GmbH, Germany; One Lambda Inc., Canoga Park, CA; Tepnel Corp., Stamford, CT; Olerup, PA; Luminex Corporation, Austin, TX; Abbot Molecular, IL etc.

The assays described above involve steps such as but not limited to, immunoblotting, immunodiffusion, immunoelectrophoresis, or immunoprecipitation. In some embodiments, an automatic analyzer (e.g., a PCR machine or an automatic sequencing machine) is used to determine the presence or absence of a SE, an allele in the HLA-DRB1*04 allelic group and/or an HLA-DRB1*SE allelic group.

Typically, once the presence or absence of a SE, an allele in the HLA-DRB1*04 allelic group and/or an HLA-DRB1*SE allelic group is determined, physicians or genetic counselors or patients or other researchers may be informed of the result. Specifically the result can be cast in a transmittable form of information that can be communicated or transmitted to other researchers or physicians or genetic counselors or patients. Such a form can vary and can be tangible or intangible. The result with regard to the presence or absence of a SE, an allele in the HLA-DRB1*04 allelic group and/or an HLA-DRB1*SE allelic group in the individual tested can be embodied in descriptive statements, diagrams, photographs, charts, images or any other visual forms. For example, images of gel electrophoresis of PCR products can be used in explaining the results. Diagrams showing where a variant occurs in an individual's HLA-DRB1*04 allelic group and/or an HLA-DRB1*SE allelic group are also useful in indicating the testing results. The statements and visual forms can be recorded on a tangible media such as papers, computer readable media such as floppy disks, compact disks, etc., or on an intangible media, e.g., an electronic media in the form of email or website on internet or intranet. In addition, the result with regard to the presence or absence of a SE, an allele in the HLA-DRB1*04 allelic group and/or an HLA-DRB1*SE allelic group in the individual tested can also be recorded in a sound form and transmitted through any suitable media, e.g., analog or digital cable lines, fiber optic

cables, etc., via telephone, facsimile, wireless mobile phone, internet phone and the like. All such forms (tangible and intangible) would constitute a “transmittable form of information”. Thus, the information and data on a test result can be produced anywhere in the world and transmitted to a different location. For example, when a genotyping assay is conducted offshore, the information and data on a test result may be generated and cast in a transmittable form as described above.

The test result in a transmittable form thus can be imported into the U.S. Accordingly, the present disclosure also encompasses a method for producing a transmittable form of information on the presence or absence of a SE, an allele in the HLA-DRB1*04 allelic group and/or an HLA-DRB1*SE allelic group in an individual. This form of information is useful for predicting the responsiveness of a patient having RA to treatment with an IL-17 antagonist.

Disclosed herein are methods of predicting the likelihood that a patient having rheumatoid arthritis (RA) will respond to treatment with an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof), comprising assaying a biological sample from the patient for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group, wherein the presence of the at least one allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the at least one allele is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.

Disclosed herein are methods of predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof), comprising: a) obtaining a biological sample from said patient; and b) assaying the biological sample for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group, wherein the presence of the at least one allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the at least one allele is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.

Disclosed herein are methods of predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g.,

IL-17 antibody or antigen binding fragment thereof), comprising assaying a biological sample from the patient for the presence or absence of a shared epitope (SE), wherein the presence of the SE is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the SE is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.

Disclosed herein are methods of predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof), comprising: a) obtaining a biological sample from said patient; and b) assaying the biological sample for the presence or absence of a SE, wherein the presence of the SE is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the SE is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.

Disclosed herein are methods for determining the responsiveness of a patient having RA to treatment with an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof), comprising: a) performing an assay on a biological sample from the patient to determine the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and b) assigning the patient as responsive to treatment with the IL-17 antagonist if the presence of the at least one allele is detected in the sample.

Disclosed herein are methods for determining the responsiveness of a patient having RA to treatment with an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof), comprising: a) performing an assay on a biological sample from the patient to determine the presence or absence of a SE; and b) assigning the patient as responsive to treatment with the IL-17 antagonist if the presence of the at least one allele is detected in the sample.

Disclosed herein are methods of predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof), comprising assaying a biological sample

from the patient for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group using an automatic analyzer, wherein the presence of the at least one allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the at least one allele is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 binding molecule.

Disclosed herein are methods of predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof), comprising assaying a biological sample from the patient for the presence or absence of a SE using an automatic analyzer, wherein the presence of the SE is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the SE is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.

Disclosed herein are methods for producing a transmittable form of information for use in predicting the responsiveness of a patient having RA to treatment with an IL-17 antagonist, comprising: a) assaying a biological sample from the patient for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and b) embodying the result of the assaying step in a transmittable form of information.

Disclosed herein are methods for producing a transmittable form of information for use in predicting the responsiveness of a patient having RA to treatment with an IL-17 antagonist, comprising: a) assaying a biological sample from the patient for the presence or absence of a SE; and b) embodying the result of the assaying step in a transmittable form of information.

Disclosed herein are also *in vitro* test methods for selecting a patient for treatment of RA, comprising determining if the patient has the presence or absence of at least one allele in the HLA-DRB1*04 allelic group, the presence or absence of at least one allele in the HLA-DRB1*SE allelic group or the SE. In some embodiments, a patient who has the SE, or an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group has an improved therapeutic response to the following regimen: a) administering the patient three doses of about 10 mg/kg of an IL-17 antagonist, the first dose being delivered during week zero, the second dose being delivered during week two, and the third dose being delivered during week four; and a) thereafter administering the patient about 75 mg - about 300 mg of the IL-17

antagonist twice a month, monthly, every two months or every three months, beginning during week eight.

In some embodiments of the above methods, the presence of two alleles in the HLA-DRB1*04 allelic group in the biological sample is indicative of a further increased likelihood that the patient will respond to treatment with the IL-17 antagonist. In some embodiments, the presence of two alleles in the HLA-DRB1*SE allelic group in the biological sample is indicative of a further increased likelihood that the patient will respond to treatment with the IL-17 antagonist.

In some embodiments, the presence or absence of the SE is detected by assaying the biological sample for the presence or absence of at least one allele in the HLA-DRB1*SE allelic group.

In some embodiments, the presence or absence of the at least one allele is detected by assaying the biological sample for a genomic sequence of the at least one allele, a product of the at least one allele, or an equivalent genetic marker of the at least one allele.

In some embodiments, the presence or absence of the SE, the at least one allele in the HLA-DRB1*04 allelic group, or the at least one allele in the HLA-DRB1*SE allelic group is detected by a technique selected from the group consisting of Northern blot analysis, reverse transcription-polymerase chain reaction (RT-PCR), RT-PCR ELISA, TaqMan-based quantitative RT-PCR (probe-based quantitative RT-PCR), SYBR green-based quantitative RT-PCR, polymerase chain reaction (PCR), direct sequencing, Sequence Specific Oligonucleotide (SSO) hybridization, Sequence Specific Primer (SSP) typing, and Sequence Based Typing (SBT), Southern blot, quantitative PCR (probe- or SYBR green-based), an immunoassay, immunohistochemistry, ELISA, flow cytometry, Western blot, HPLC, and mass spectrometry.

In some embodiments, the biological sample is selected from the group consisting of synovial fluid, blood, serum, plasma, urine, tear, saliva, cerebrospinal fluid, leukocyte sample and a tissue sample.

In some embodiments, the patient is a high risk RA patient.

Methods of Treatment and Uses of IL-17 Antagonists

The disclosed IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g.,

IL-17 antibody or antigen binding fragment thereof) are useful for the treatment, prevention, or amelioration of RA (e.g., signs and symptoms & structural changes, preventing further joint erosion, improving joint structure, etc.), particularly in RA patients of having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group.

The IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof), may be used *in vitro*, *ex vivo*, or incorporated into pharmaceutical compositions and administered to individuals (e.g., human patients) *in vivo* to treat, ameliorate, or prevent RA, e.g., in RA patients having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group. 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 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof), 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 antagonist, 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 composition of the disclosure may be in the form of a liposome in which the IL-17 antagonist 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.

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 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof).

When a therapeutically effective amount of an IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof) 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 components such as 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 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof) is administered by intravenous, cutaneous or subcutaneous injection, the IL-17 antagonist 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 antagonist, an isotonic vehicle such as sodium chloride, Ringer's, dextrose, dextrose and sodium chloride, lactated Ringer's, 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 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, may be 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.

Antibodies, e.g., antibodies to IL-17, are typically formulated either in aqueous form ready for parenteral administration or as lyophilisates for reconstitution with a suitable diluent prior to administration. In some embodiments of the disclosed methods and uses, the IL-17 antagonist, e.g., IL-17 antibody, e.g., secukinumab, is formulated as a lyophilisate. Suitable lyophilisate formulations can be reconstituted in a small liquid volume (e.g., 2ml or less) to allow subcutaneous administration and can provide solutions with low levels of antibody aggregation. The use of antibodies as the active ingredient of pharmaceuticals is now widespread, including the products HERCEPTIN™ (trastuzumab), RITUXAN™ (rituximab), SYNAGIS™ (palivizumab), etc. Techniques for purification of antibodies to a pharmaceutical grade are well known in the art.

The appropriate dosage will, of course, vary depending upon, for example, the particular IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof) 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 health care provider will decide the amount of the IL-17 antagonist with which to treat each individual patient. In some embodiments, the attending health care provider may administer low doses of the IL-17 antagonist and observe the patient's response. In other embodiments, the initial dose(s) of IL-17 antagonist administered to a patient are high, and then are titrated downward until signs of relapse occur. Larger doses of the IL-17 antagonist may be administered until the optimal therapeutic effect is obtained for the patient, and 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. 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 health care provider will decide on the appropriate duration of i.v. or s.c. therapy and the timing of administration of the therapy, using the pharmaceutical composition of the present disclosure.

Preferred dosing and treatment regimens for treating RA patients having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group are provided in **Table 3**:

<u>i.v. induction (3 x 10 mg/kg every other week)</u>	<u>s.c. maintenance regimen (75 mg, 150 mg, 300 mg)</u>
• first dose = during week 0 • second dose = during week 2 • third dose = during week 4	• first monthly dose = during week 8 • every month (about 4 weeks) thereafter.
<u>i.v. induction (3 x 10 mg/kg every three weeks)</u>	<u>s.c. maintenance regimen (75 mg, 150 mg, 300 mg)</u>
• first dose = during week 0 • second dose = during week 3 • third dose = during week 6	• first monthly dose = during week 10 • every month (about 4 weeks) thereafter
<u>i.v. induction (3 x 10 mg/kg every month)</u>	<u>s.c. maintenance regimen (75 mg, 150 mg, 300 mg)</u>
• first dose = during week 0 • second dose = during week 4 • third dose = during week 8	• first monthly dose = during week 12 • every month (about 4 weeks) thereafter
<u>i.v. induction (2 x 10 mg/kg every other week)</u>	<u>s.c. maintenance regimen (75 mg, 150 mg, 300 mg)</u>
• first dose = during week 0 • second dose = during week 2	• first monthly dose = during week 6 • every month (about 4 weeks) thereafter
<u>i.v. induction (2 x 10 mg/kg every three week)</u>	<u>s.c. maintenance regimen (75 mg, 150 mg, 300 mg)</u>
• first dose = during week 0 • second dose = during week 3	• first monthly dose = during week 7 • every month (about 4 weeks) thereafter
<u>i.v. induction (2 x 10 mg/kg every month)</u>	<u>s.c. maintenance regimen (75 mg, 150 mg, 300 mg)</u>
• first dose = during week 0 • second dose = during week	• first monthly dose = during week 8 • every month (about 4 weeks) thereafter.
<u>S.C. induction (4 x 10 mg/kg weekly s)</u>	<u>s.c. maintenance regimen (75 mg, 150 mg, 300 mg)</u>
• first weekly dose = during week 0 • second weekly dose = during week 1 • third weekly dose = during week 2 • fourth weekly dose = during week 3	• first monthly dose = during week 7 • every month (about 4 weeks) thereafter
<u>S.C. induction (10 mg/kg daily)</u>	<u>s.c. maintenance regimen (75 mg, 150 mg, 300 mg)</u>
• dose 1-7 = day 1-7	• first monthly dose = during week 4 or 5 • every month (about 4 weeks) thereafter
<u>S.C. induction (5 x 10 mg/kg weekly)</u>	<u>s.c. maintenance regimen (75 mg, 150 mg, 300 mg)</u>
• first weekly dose = during week 0 • second weekly dose = during week 1 • third weekly dose = during week 2 • fourth weekly dose = during week 3 • fifth weekly dose = during week 4	• first monthly dose = during week 8 • every month (about 4 weeks) thereafter

Table 3: Preferred Dosing Regimens for treating RA patients.

The timing of dosing is generally measured from the day of the first dose of the active compound (e.g., secukinumab), which is also known as “baseline”. However, different health care providers use different naming conventions, as shown in **Table 4**, below.

Week	0/1	1/2	2/3	3/4	4/5	5/6	6/7	7/8	8/9	Etc.
1st day	0/1	7/8	14/15	21/22	28/29	35/36	42/43	49/50	56/57	Etc.

Table 4 – Common naming conventions for dosing regimens. Bolded items refer to the naming convention used herein.

For consistency, as used herein, the first week of dosing will be referred to as week zero, while the first day of dosing will be referred to as day 1. Thus, as an example, four loading doses of secukinumab administered weekly during an induction regimen would be provided during week 0 (e.g., on about day 1), during week 1 (e.g., on about day 8), during week 2 (e.g., on about day 15), and during week 3 (e.g., on about day 22). It will be understood that a dose need not be provided at an exact time point, e.g., a dose due on day 29 could be provided, e.g., on day 24 to day 34.

It will be understood that dose escalation may be required (e.g., during the induction and/or maintenance phase) for certain patients, e.g., patients that display inadequate response to treatment with the IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen binding fragment thereof). Thus, s.c. dosages of secukinumab may be greater than about 75 mg to about 300 mg s.c., e.g., about 80 mg, about 100 mg, about 125 mg, about 175 mg, about 200 mg, about 250 mg, about 350 mg, about 400 mg, etc.; similarly, i.v. dosages may be greater than about 10 mg/kg, e.g., about 11 mg/kg, 12 mg/kg, 15 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, etc. It will also be understood that dose reduction may also be required (e.g., during the induction and/or maintenance phase) for certain patients, e.g., patients that display adverse events or an adverse response to treatment with the IL-17 antagonist (e.g., secukinumab). Thus, dosages of secukinumab may be less than about 75 mg to about 300 mg s.c., e.g., about 25 mg, about 50 mg, about 80 mg, about 100 mg, about 125 mg, about 175 mg, about 200 mg, 250 mg, etc.; similarly, i.v. dosages may be less than about 10 mg/kg, e.g., about 9 mg/kg, 8 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, 1 mg/kg etc.

Disclosed herein are methods of treating rheumatoid arthritis (RA), comprising: a) obtaining a biological sample from an RA patient; and b) assaying the biological sample for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and c) administering a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumb) to the RA patient if the biological sample has the presence of the at least one allele.

Disclosed herein are methods of treating RA, comprising: a) assaying a biological sample from an RA patient for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and b) administering a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumb) to the RA patient if the biological sample has the presence of the at least one allele.

Disclosed herein are methods of selectively treating a patient having RA, comprising: a) determining whether a biological sample from the patient has the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and b) administering a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumb) to the RA patient if the biological sample has the presence of the at least one allele.

Disclosed herein are methods of treating an RA patient, comprising: a) receiving data regarding the presence or absence in a biological sample obtained from said patient of at least one allele in the HLA-DRB1*04 allelic group; and b) administering an IL-17 antagonist (e.g., secukinumb) to the patient if said received data indicates that the patient has the at least one allele.

Disclosed herein are methods of treating RA, comprising: a) obtaining a biological sample from an RA patient; and b) assaying the biological sample for the presence or absence of a shared epitope (SE); and c) administering a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumb) to the RA patient if the biological sample has the presence of the SE.

Disclosed herein are methods of treating RA, comprising: a) assaying a biological sample from an RA patient for the presence or absence of a SE; and b) administering a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumb) to the RA patient if the biological sample has the presence of the SE.

Disclosed herein are methods of selectively treating a patient having RA, comprising: a) determining whether a biological sample from the patient has the presence or absence of a SE;

and b) administering a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumab) to the RA patient if the biological sample has the presence of the SE.

Disclosed herein are methods of treating an RA patient, comprising: a) receiving data regarding the presence or absence in a biological sample obtained from said patient of a SE; and b) administering an IL-17 antagonist (e.g., secukinumab) to the patient if said received data indicates that the patient has the at least one allele.

Disclosed herein are methods of treating RA, comprising: a) selecting an RA patient for treatment on the basis of the RA patient having at least one allele in the HLA-DRB1*04 allelic group; and b) administering a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumab) to the RA patient.

Disclosed herein are methods of treating RA, comprising administering an IL-17 antagonist (e.g., secukinumab) to an RA patient that has an increased likelihood of responding to said IL-17 antagonist, wherein said increased likelihood is determined on the basis of the patient having at least one allele in the HLA-DRB1*04 allelic group.

Disclosed herein are methods of treating RA, comprising administering an IL-17 antagonist (e.g., secukinumab) to an RA patient that has an increased likelihood of responding to said IL-17 antagonist, wherein said increased likelihood is identified by the predictive methods herein.

Disclosed herein are methods of treating RA, comprising administering a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumab) to an RA patient, provided that the RA patient has at least one allele in the HLA-DRB1*04 allelic group.

Disclosed herein are methods of treating RA, comprising: a) selecting an RA patient for treatment on the basis of the RA patient having a SE; and b) administering a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumab) to the RA patient.

Disclosed herein are methods of treating RA, comprising administering an IL-17 antagonist (e.g., secukinumab) to an RA patient that has an increased likelihood of responding to said IL-17 antagonist, wherein said increased likelihood is determined on the basis of the patient having the SE.

Disclosed herein are methods of treating RA, comprising administering an IL-17 antagonist (e.g., secukinumab) to an RA patient that has an increased likelihood of responding to

said IL-17 antagonist, wherein said increased likelihood is identified by any of the methods disclosed herein.

Disclosed herein are methods of treating RA, comprising administering a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumb) to an RA patient, provided that the RA patient has a SE.

In some embodiments, the step of administering comprises intravenously administering three doses of about 10 mg/kg of the IL-17 antagonist (e.g., secukinumb) to said patient, each of said doses being administered every other week. In some embodiments, the step of administering comprises subcutaneously administering the patient about 75 mg - about 300 mg of the IL-17 antagonist twice a month, monthly, every two months or every three months.

Disclosed herein are also IL-17 antagonists (e.g., secukinumb) for use in treating RA, characterized in that: a) a biological sample is obtained from an RA patient; b) the biological sample is assayed for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and c) a therapeutically effective amount of an IL-17 antagonist is administered to the RA patient if the biological sample has the presence of the at least one allele.

Disclosed herein are IL-17 antagonists (e.g., secukinumb) for use in treating RA, characterized in that: a) a biological sample from an RA patient is assayed for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and b) a therapeutically effective amount of an IL-17 antagonist is administered to the RA patient if the biological sample has the presence of the at least one allele.

Disclosed herein are IL-17 antagonists (e.g., secukinumb) for use in treating RA, characterized in that: a) a biological sample is obtained from an RA patient; b) the biological sample is assayed for the presence or absence of the SE; and c) a therapeutically effective amount of an IL-17 antagonist is administered to the RA patient if the biological sample has the presence of the at least one allele.

Disclosed herein are IL-17 antagonists (e.g., secukinumb) for use in treating RA, characterized in that: a) a biological sample from an RA patient is assayed for the presence or absence of a SE; and b) a therapeutically effective amount of an IL-17 antagonist is administered to the RA patient if the biological sample has the presence of the at least one allele.

Disclosed herein are IL-17 antagonists (e.g., secukinumb) for use in treating RA, characterized in that: a) an RA patient is selected for treatment on the basis of the RA patient

having at least one allele in the HLA-DRB1*04 allelic group; and b) a therapeutically effective amount of an IL-17 binding molecule is administered to the RA patient.

Disclosed herein are IL-17 antagonists (e.g., secukinumb) for use in treating a patient having RA, characterized in that the IL-17 antagonist is to be administered to a patient that has at least one allele in the HLA-DRB1*04 allelic group.

Disclosed herein are IL-17 antagonists (e.g., secukinumb) for use in treating a patient having RA, characterized in that the IL-17 antagonist is to be administered to a patient selected for treatment on the basis of having at least one allele in the HLA-DRB1*04 allelic group.

Disclosed herein are IL-17 antagonists (e.g., secukinumb) for use in treating RA, characterized in that: a) an RA patient is selected for treatment on the basis of the RA patient having a SE; and b) a therapeutically effective amount of an IL-17 antagonist is administered to the RA patient.

Disclosed herein are IL-17 antagonists (e.g., secukinumb) for use in treating a patient having RA, characterized in that the IL-17 antagonist is to be administered to a patient that has a SE.

Disclosed herein are IL-17 antagonists (e.g., secukinumb) for use in treating a patient having RA, characterized in that the IL-17 antagonist is to be administered to a patient selected for treatment on the basis of having a SE.

In some embodiments, the IL-17 antagonists (e.g., secukinumb) is to be administered intravenously to a patient in need thereof as three doses of about 10 mg/kg, each of the three doses being delivered every other week. In some embodiments, the IL-17 antagonist is to be administered subcutaneously to the patient as a dose of about 75 mg - about 300 mg twice a month, monthly, every two months or every three months.

Disclosed herein are also uses of an IL-17 antagonist (e.g., secukinumb) in the manufacture of a medicament for use in treating a patient having RA, wherein the RA patient has at least one allele in the HLA-DRB1*04 allelic group.

Disclosed herein are uses of an IL-17 antagonist (e.g., secukinumb) in the manufacture of a medicament for use in treating a patient having RA, wherein the RA patient is selected for treatment on the basis of having at least one allele in the HLA-DRB1*04 allelic group.

Disclosed herein are uses of an IL-17 antagonist (e.g., secukinumb) in the manufacture of a medicament for use in treating a patient having RA, wherein the RA patient has the SE.

Disclosed herein are uses of an IL-17 antagonist (e.g., secukinumab) in the manufacture of a medicament for use in treating a patient having RA, wherein the RA patient is selected for treatment on the basis of having a SE.

Disclosed herein are uses of an IL-17 antagonist in preparation of a medicament for the treatment of RA, provided that the patient is selected for the treatment on the basis of having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group.

Disclosed herein are uses of an IL-17 antagonist for the manufacture of a medicament for the treatment of RA in a patient characterized as having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group, wherein the medicament is formulated to comprise containers, each container having a sufficient amount of the IL-17 antagonist to allow delivery of at least about 75 mg – about 150 mg IL-17 antagonist per unit dose.

Disclosed herein are uses of an IL-17 antagonist for the manufacture of a medicament for the treatment of RA in a patient characterized as having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group, wherein the medicament is formulated to comprise containers, each container having a sufficient amount of the IL-17 antagonist to allow delivery of at least about 10 mg IL-17 antagonist/kg patient weight per unit dose.

Disclosed herein are uses of an IL-17 antagonist for the manufacture of a medicament for the treatment of RA in a patient characterized as having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group, wherein the medicament is formulated at a dosage to allow intravenous delivery of about 10 mg IL-17 antagonist/kg patient weight per unit dose.

Disclosed herein are uses of an IL-17 antagonist for the manufacture of a medicament for the treatment of RA in a patient characterized as having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group, wherein the medicament is formulated at a dosage to allow subcutaneous delivery of about 75 mg – about 150 mg IL-17 antagonist per unit dose.

As used herein, the phrase “container having a sufficient amount of the IL-17 antagonist to allow delivery of [a designated dose]” is used to mean that a given container (e.g., vial, pen,

syringe) has disposed therein a volume of an IL-17 antagonist (e.g., as part of a pharmaceutical composition) that can be used to provide a desired dose. As an example, if a desired dose is 75 mg, then a clinician may use 2 ml from a container that contains an IL-17 antibody formulation with a concentration of 37.5 mg/ml, 1 ml from a container that contains an IL-17 antibody formulation with a concentration of 75 mg/ml, 0.5 ml from a container contains an IL-17 antibody formulation with a concentration of 150 mg/ml, etc. In each such case, these containers have a sufficient amount of the IL-17 antagonist to allow delivery of the desired 75 mg dose.

As used herein, the phrase “formulated at a dosage to allow [route of administration] delivery of [a designated dose]” is used to mean that a given pharmaceutical composition can be used to provide a desired dose of an IL-17 antagonist, e.g., an IL-17 antibody, e.g., secukinumab, via a designated route of administration (e.g., s.c. or i.v.). As an example, if a desired subcutaneous dose is 75 mg, then a clinician may use 2 ml of an IL-17 antibody formulation having a concentration of 37.5 mg/ml, 1 ml of an IL-17 antibody formulation having a concentration of 75 mg/ml, 0.5 ml of an IL-17 antibody formulation having a concentration of 150 mg/ml, etc. In each such case, these IL-17 antibody formulations are at a concentration high enough to allow subcutaneous delivery of the IL-17 antibody. Subcutaneous delivery typically requires delivery of volumes of less than about 2 ml, preferably a volume of about 1ml or less.

In some embodiments, the presence or absence of the SE is detected by assaying the biological sample for the presence or absence of at least one allele in the HLA-DRB1*SE allelic group.

In some embodiments, the presence or absence of the at least one allele is detected by assaying the biological sample for a genomic sequence of the at least one allele, a product of the at least one allele, or an equivalent genetic marker of the at least one allele.

In some embodiments, the presence or absence of the SE, the at least one allele in the HLA-DRB1*04 allelic group, or the at least one allele in the HLA-DRB1*SE allelic group is detected by a technique selected from the group consisting of Northern blot analysis, reverse transcription-polymerase chain reaction (RT-PCR), RT-PCR ELISA, TaqMan-based quantitative RT-PCR (probe-based quantitative RT-PCR), SYBR green-based quantitative RT-PCR, polymerase chain reaction (PCR), direct sequencing, Sequence Specific Oligonucleotide (SSO) hybridization, Sequence Specific Primer (SSP) typing, and Sequence Based Typing (SBT),

Southernblot, quantitative PCR (probe- or SYBR green-based), an immunoassay, immunohistochemistry, ELISA, flow cytometry, Western blot, HPLC, and mass spectrometry.

In some embodiments, the biological sample is selected from the group consisting of synovial fluid, blood, serum, plasma, urine, tear, saliva, cerebrospinal fluid, leukocyte sample and a tissue sample.

In some embodiments, the patient is a high risk RA patient.

Combination Therapies for the Treatment of RA

In practicing the methods of treatment or uses of the present disclosure, a therapeutically effective amount of an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof) is administered to a patient, e.g., a mammal (e.g., a human). An IL-17 antagonist (e.g., secukinumab) may be administered in accordance with the method of the disclosure either alone or in combination with other agents and therapies for treating RA patients having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group, e.g., in combination with at least one anti-rheumatic agent, such as an immunosuppressive agent, a disease-modifying anti-rheumatic drug (DMARD), a pain-control drug, a steroid, a non-steroidal anti-inflammatory drug (NSAID), a cytokine antagonist, a bone anabolic, a bone anti-resorptive, and combinations thereof (e.g., dual and tripple therapies). When coadministered with one or more additional agents, an IL-17 antagonist 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 antagonist in combination with other agents.

Non-steroidal anti inflammatory drugs and pain control agents useful in combination with secukinumab for the treatment of RA patients include, propionic acid derivative, acetic acid derivative, enolic acid derivatives, fenamic acid derivatives, Cox inhibitors, e.g., lumiracoxib, ibuprophen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin, indomethacin, sulindac, etodolac, ketorolac, nabumetone, aspirin, naproxen, valdecoxib, etoricoxib, MK0966; rofecoxib, acetaminophen, Celecoxib, Diclofenac, tramadol, piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam, mefanamic acid, meclofenamic acid, flufenamic acid, tolfenamic, valdecoxib, parecoxib, etodolac, indomethacin, aspirin, ibuprophen, firocoxib. DMARDs useful

in combination with an IL-17 antagonist, e.g., secukinumab, for the treatment of RA patients of having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group include, methotrexate (MTX), antimalarial drugs (e.g., hydroxychloroquine and chloroquine), sulfasalazine, Leflunomide, azathioprine, cyclosporin, gold salts, minocycline, cyclophosphamide, D-penicillamine, minocycline, auranofin, tacrolimus, mycristin, chlorambucil. Steroids (e.g., glucocorticoids) useful in combination with an IL-17 antagonist, e.g., secukinumab, for the treatment of RA patient having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group include, Prednisolone, Prednisone, dexamethasone, cortisol, cortisone, hydrocortisone, methylprednisolone, betamethasone, triamcinolone, beclometasone, fludrocortisone, deoxycorticosterone, aldosterone.

Biologic agents useful in combination with an IL-17 antagonist, e.g., secukinumab, for the treatment of RA patients having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group, ADALIMUMAB (Humira®), ETANERCEPT (Enbrel®), INFLIXIMAB (Remicade®; TA-650), CERTOLIZUMAB PEGOL (Cimzia®; CDP870), GOLIMUMAB (Simponi®; CNT0148), ANAKINRA (Kineret®), RITUXIMAB (Rituxan®; MabThera®), ABATACEPT (Orencia®), TOCILIZUMAB (RoActemra /Actemra®), integrin antagonists (TYSABRI® (natalizumab)), IL-1 antagonists (ACZ885 (Ilaris), Anakinra (Kineret®)), CD4 antagonists, further IL-17 antagonists (LY2439821, RG4934, AMG827, SCH900117, R05310074, MEDI-571, CAT-2200), IL-23 antagonists, IL-20 antagonists, IL-6 antagonists, TNF alpha antagonists (e.g., TNF alpha antagonists or TNF alpha receptor antagonists, e.g., pegsunercept, etc.), BLYS antagonists (e.g., Atacicept, Benlysta®/ LymphoStat-B® (belimumab)), P38 Inhibitors, CD20 antagonists (Ocrelizumab, Ofatumumab (Arzerra®)), Interferon gamma antagonists (Fontolizumab).

Other agents useful in combination with an IL-17 antagonist, e.g., secukinumab, for the treatment of RA patients having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group include, SB-681323, Rob 803, AZD5672, AD 452, SMP 114, HZT-501, CP-195,543, Doxycycline, vancomycin, CRx-102, AMG108, pioglitazone, SBI-087, SCIO-469, Cura-100, Oncoxin + Viusid, TwHF, PF-04171327, AZD5672, Methoxsalen, ARRY-438162, Vitamin D – ergocalciferol, Milnacipran, Paclitaxel, GW406381, rosiglitazone, SC12267 (4SC-101); LY2439821, BTT-1023, ERB-041, ERB-041, KB003, CF101, ADL5859, MP-435, ILV-094, GSK706769, GW856553, ASK8007, MOR103, HE3286, CP-690,550

(tasocitinib), REGN88 (SAR153191), TRU-015, BMS-582949, SBI-087, LY2127399, E-551S-551, H-551, GSK3152314A, RWJ-445380, Tacrolimus (Prograf®), RAD001, rapamune, rapamycin, fostamatinib, Fentanyl, XOMA 052, CNTO 136, JNJ 38518168, Imatinib, ATN-103, ISIS 104838, folic acid, folate, TNFa kinoid, MM-093, type II collagen, VX-509, AMG 827 70, masitinib (AB1010), LY2127399, cyclosporine, SB-681323, MK0663, NNC 0151-0000-0000, ATN-103, CCX 354-C, CAM3001, LX3305, Cetrorelix, MDX-1342, TMI-005, MK0873, CDP870, Tranilast, CF101, mycophenolic acid (and esters thereof), VX-702, GLPG0259, SB-681323, BG9924, ART621, LX3305, T-614, Fostamatinib disodium (R935788), CCI-779, ARRY-371797, CDP6038, AMG719, BMS-582949, GW856553, rosiglitazone, CH-4051, CE-224,535, GSK1827771, GW274150, BG9924, PLX3397, TAK-783, INCB028050, LY2127399, LY3009104, R788, Curcumin (Longvida™), Rosuvastatin, PRO283698, AMG 714, MTRX1011A, Maraviroc, MEDI-522, MK0663, STA 5326 mesylate, CE-224,535, AMG108, BG00012, ramipril, VX-702, CRx-102, LY2189102, SBI-087, SB-681323, CDP870, Milnacipran, PD 0360324, PH-797804, AK106-001616, PG-760564, PLA-695, MK0812, ALD518, Cobiprostone, somatropin, tgAAC94 gene therapy vector, MK0359, GW856553, esomeprazole, everolimus, trastuzumab, bone anabolics and bone anti-resorptives (e.g., PTH, bisphosphonates (e.g., zoledronic acid), JAK1 and JAK2 inhibitors, pan JAK inhibitors, e.g., tetracyclic pyridone 6 (P6), 325, PF-956980, sclerostin antagonists (e.g., BPS804)), denosumab, IL-6 antagonists, CD20 antagonists, CTLA4 antagonists, , IL-8 antagonists, IL-21 antagonists, IL-22 antagonist, integrin antagonists (Tysabri® (natalizumab)), sclerostin antagonists, VEGF antagonists, CXCL antagonists, MMP antagonists, defensin antagonists, IL-1 antagonists (including IL-1 beta antagonists), and IL-23 antagonists (e.g., receptor decoys, antagonistic antibodies, etc.).

A skilled artisan will be able to discern the appropriate dosages of the above agents for co-delivery with secukinumab.

Kits and Probes

The invention also encompasses kits for detecting a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group in a biological sample (a test sample) from a patient. Such kits can be used to predict if a patient having RA is likely to respond (or have a higher response) to treatment with an IL-17 IL-17 antagonist, e.g., IL-17

binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof). For example, the kit can comprise a probe (e.g., an oligonucleotide, antibody, labeled compound or other agent) capable of detecting a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group, products of those alleles and/or an equivalent genetic marker of those alleles in a biological sample.

Probes can be oligonucleotide or conjugated oligonucleotide that specifically hybridizes to a particular region within the HLA allele genetic marker; a PCR primer, together with another primer, for amplifying a particular region within said HLA allele genetic marker; an antibody recognizing an HLA allele genetic marker and/or a polypeptide product of said HLA allele genetic marker, etc. Optionally, the kit can contain a probe that targets an internal control allele, which can be any allele presented in the general population. Detection of an internal control allele is designed to assure the performance of the kit. The disclosed kits can also comprise, e.g., a buffering agent, a preservative, or a protein stabilizing agent. The kit can also comprise components necessary for detecting the detectable agent (e.g., an enzyme or a substrate). The kit can also contain a control sample or a series of control samples that can be assayed and compared to the test sample contained. Each component of the kit is usually enclosed within an individual container, and all of the various containers are within a single package along with instructions for its use.

Such kits may also comprise an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof) (e.g., in liquid or lyophilized form) or a pharmaceutical composition comprising the IL-17 antagonist (described *supra*). Additionally, such kits may comprise means for administering the IL-17 antagonist (e.g., a syringe or a prefilled pen) and instructions for use. These kits may contain additional therapeutic agents (described *supra*) for treating RA, e.g., for delivery in combination with the enclosed IL-17 antagonist, e.g., secukinumab.

Disclosed herein are kits for use in predicting the likelihood that a patient having rheumatoid arthritis (RA) will respond to treatment with an IL-17 antagonist (e.g., secukinumab) comprising: a) at least one probe capable of detecting the presence of at least one allele in the HLA-DRB1*04 allelic group; and b) instructions for using the probe to assay a biological sample

from the RA patient for the presence of the at least one allele, wherein the presence of the at least one allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the at least one allele is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist .

Disclosed herein are kits for use in treating a patient having RA, comprising: a) a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumab); b) at least one probe capable of detecting the presence of at least one allele in the HLA-DRB1*04 allelic group; c) instructions for using the probe to assay a biological sample from the patient for the presence of the at least one allele; d) instructions for administering the IL-17 antagonist to the patient if the biological sample from the patient has the presence of the at least one allele; e) optionally, means for administering the IL-17 binding molecule to the patient; and f) optionally, a therapeutically effective amount of at least one anti-rheumatic agent selected from the group consisting of an immunosuppressive agent, a disease-modifying anti-rheumatic drug (DMARD), a pain-control drug, a steroid, a non-steroidal anti-inflammatory drug (NSAID), a cytokine antagonist, a bone anabolic, a bone anti-resorptive, and combinations thereof.

Disclosed herein are kits for use in predicting the likelihood that a patient having RA respond to treatment with an IL-17 antagonist (e.g., secukinumab) comprising: a) at least one probe capable of detecting the presence of a shared epitope (SE); and b) instructions for using the probe to assay a biological sample from the RA patient for the presence or absence of the SE, wherein the presence of the SE is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the SE is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist .

Disclosed herein are kits for use in treating a patient having RA comprising, a) a therapeutically effective amount of an IL-17 antagonist (e.g., secukinumab); b) at least one probe capable of detecting the presence of a SE; c) instructions for using the probe to assay a biological sample from the patient for the presence or absence of the SE; d) instructions for administering the IL-17 antagonist to the patient if the biological sample from the patient has the presence of the SE; e) optionally, means for administering the IL-17 antagonist to the patient; and f) optionally, a therapeutically effective amount of at least one anti-rheumatic agent selected from the group consisting of an immunosuppressive agent, a disease-modifying anti-rheumatic drug

(DMARD), a pain-control drug, a steroid, a non-steroidal anti-inflammatory drug (NSAID), a cytokine antagonist, a bone anabolic, a bone anti-resorptive, and combinations thereof.

Disclosed herein are uses of a kit comprising at least one probe capable of detecting at least one allele in the HLA-DRB1*04 allelic group for predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist (e.g., secukinumab).

Disclosed herein are uses of kits comprising at least one probe capable of detecting a SE for predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist (e.g., secukinumab).

Disclosed herein are uses of at least one probe capable of detecting the presence of at least one allele in the HLA-DRB1*04 allelic group in a biological sample from a patient having RA for predicting the likelihood that the patient will respond to treatment with an IL-17 antagonist (e.g., secukinumab), wherein the presence of the at least one allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the at least one allele is indicative of a decreased likelihood likelihood that the patient will respond to treatment with the IL-17 antagonist.

Disclosed herein are uses of at least one probe capable of detecting the presence of a SE in a biological sample from a patient having RA for predicting the likelihood that the patient will respond to treatment with an IL-17 antagonist (e.g., secukinumab), wherein the presence of the at least one allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the at least one allele is indicative of a decreased likelihood likelihood that the patient will respond to treatment with the IL-17 antagonist.

Disclosed herein are kits comprising: a) a pharmaceutical composition comprising an IL-17 antagonist (e.g., secukinumab) for use in the treatment of rheumatoid arthritis (RA) in a patient; and b) instructions describing how to administer said pharmaceutical composition to the patient, wherein the patient is characterized as having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group.

In some embodiments, the probe is capable of detecting the presence of at least one allele in the HLA-DRB1*SE allelic group.

In some embodiments, the probe is an oligonucleotide that specifically hybridizes to a region of a nucleic acid coding for the at least one allele, an antibody that detects a polypeptide

product of the at least one allele, or an oligonucleotide that specifically hybridizes to a region of a nucleic acid coding for an equivalent genetic marker of the at least one allele.

In some embodiments, the presence of the SE is detected by assaying the biological sample for the presence of at least one allele in the HLA-DRB1*SE allelic group.

In some embodiments, the presence of two alleles in the HLA-DRB1*SE allelic group in the biological sample is indicative of a further increased likelihood that the patient will respond to treatment with the IL-17 antagonist (e.g., secukinumab).

In some embodiments, the presence of two alleles in the HLA-DRB1*04 allelic group in the biological sample is indicative of a further increased likelihood that the patient will respond to treatment with the IL-17 antagonist (e.g., secukinumab).

In some embodiments, the presence or absence of the at least one allele is detected by assaying the biological sample for a genomic sequence of the at least one allele, a product of the at least one allele, or an equivalent genetic marker of the at least one allele.

In some embodiments, the biological sample is selected from the group consisting of synovial fluid, blood, serum, plasma, urine, tear, saliva, cerebrospinal fluid, leukocyte sample and a tissue sample.

In some embodiments, the patient is a high risk RA patient.

General

In preferred embodiments of the disclosed methods, uses, pharmaceutical compositions, kits, assays, and treatment regimens, the IL-17 antagonist is selected from the group consisting of: a) an IL-17 binding molecule or an IL-17 receptor binding molecule; b) secukinumab; c) an IL-17 antibody that binds to an epitope of IL-17 comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129; d) an IL-17 antibody that binds to an epitope of IL-17 comprising Tyr43, Tyr44, Arg46, Ala79, Asp80; e) an IL-17 antibody that binds to an epitope of an IL-17 homodimer having two mature IL-17 protein chains, said epitope comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129 on one chain and Tyr43, Tyr44, Arg46, Ala79, Asp80 on the other chain; f) an IL-17 antibody that binds to an epitope of an IL-17 homodimer having two mature IL-17 protein chains, said epitope comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129 on one chain and Tyr43, Tyr44, Arg46, Ala79, Asp80 on the other chain, wherein the IL-

17 binding molecule has a K_D of about 100-200 pM, and wherein the IL-17 binding molecule has an *in vivo* half-life of about 4 weeks; and g) an IL-17 antibody that comprises an antibody selected from the group consisting of: 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; and 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.

In the above-mentioned methods, therapeutic regimens, uses, and pharmaceutical compositions, more preferred embodiments employ an IL-17 binding molecule, even more preferred embodiments employ a human antibody to IL-17, and the most preferred embodiments employ secukinumab.

All patents, published patent applications, publications, references and other material referred to herein are incorporated by reference herein in their entirety. The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by

one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated by reference. The following Examples are presented in order to more fully illustrate the preferred embodiments of the disclosure. These examples should in no way be construed as limiting the scope of the disclosed patient matter, as defined by the appended claims.

EXAMPLES

Example 1: Use of secukinumab to treat RA (Studies A2101 and F2201)

Example 1.1 – A2101 Proof of concept study and results.

Clinical study A2101 was a single and multiple-dose, placebo controlled, double-blind proof-of-concept study to assess safety and pharmacokinetics of secukinumab in patients with active RA on a stable dose of methotrexate. The trial was included 96 rheumatoid arthritis patients and 8 healthy volunteers. The trial was divided into 3 parts and doses were escalated from 1 x 0.3 mg/kg to 2 x 10 mg/kg i.v.

The primary efficacy analysis was based on 52 patients who were randomized to receive two infusions of either 10 mg/kg secukinumab (n=26) or placebo (n=26). The efficacy population comprised male and female patients with active RA on concomitant MTX. The primary endpoint of the study was ACR20 response rate at 6 weeks. Secondary endpoints included other timepoints and the DAS28 response. At the primary end point of 6 weeks, the ACR20 response rate was 46% for secukinumab 2x10mg/kg compared with 27% for placebo [$\Delta=19\%$; P value = 0.13]. ACR50 and ACR70 response rates on secukinumab were 27% [$\Delta=12\%$] and 8% [$\Delta=0\%$], respectively. DAS28 decreased over time with greater reductions on secukinumab 2x10mg/kg compared with placebo. Response to treatment was rapid. Percentage of ACR20 responder rates at week 4 were 50% for secukinumab and 31% for placebo, and at week 16 were 54% for AIN4 secukinumab 57 and 31% for placebo. Although numbers were low in the other dose arms, analysis of patients receiving the 2 x 1 mg (n = 6) and 3 x 1 mg (n = 6) indicated that these doses may also be effective for the treatment of RA.

Example 1.2 - F2201 study design

Eligible patients (i.e., fulfilling ACR 1987 revised classification criteria for RA for at least 3 months) were required to present active RA defined by ≥ 6 out of 28 tender joints and ≥ 6 out of 28 swollen joints, and hsCRP ≥ 10 mg/L or ESR ≥ 28 mm/1st hour (mm/h) at the time of randomization to assure ability to detect response to treatment using ACR criteria. Eligible candidates were on MTX for at least 3 months and at selection were currently treated with a stable weekly dose of MTX (≥ 7.5 mg/week - ≤ 25 mg/week) for at least 4 weeks. Adult RA patients (n=237) on methotrexate were randomized equally to receive monthly s.c. injections of secukinumab 25mg, 75mg, 150mg, 300mg or placebo. Patients with previous exposure to biologics were included in all cohorts (18 – 22%). The primary end point was the proportion of patients achieving American College of Rheumatology (ACR) 20 at week 16. At Week 20 (Visit 8), patients who were randomized to placebo at Week 0 or who were randomized to secukinumab but did not achieve an ACR20 response at Week 16 were re-assigned to receive double blind treatment up to Week 48, with a final efficacy assessment performed at Week 52, and a follow up visit at Week 60, as follows starting at Week 20:

Patients on active treatment who were responders continued on their dose regimen;

- All placebo patients were switched to active treatment 150 mg s.c. q4wk (monthly), independent of disease activity;
- All patients treated with 25 mg or 75 mg secukinumab q4wk who were non-responders were switched to 150 mg s.c. q4wk;
- Non-responders in the 150 mg group were switched to the next highest dose - 300 mg s.c. q4wk;
- All patients on 300 mg group remained on their respective dose to assess if exposure longer than 16 weeks will induce a clinical response in these patients.

The primary efficacy variable is the clinical response to treatment according to ACR20 individual improvement in disease activity at Week 16 (for information on ACR scores, see Felson et al. (1995) *Arthritis Rheum*; 38(6):727-35). Results are assessed by the proportion of patients achieving the ACR20 response criteria at Week 16.

Additional measures include ACR50 (50 % improvement in item B (above) in at least 3 of 5 measures and 50 % improvement in the swollen and tender joint count), ACR70 (70 % improvement in item B (above) in at least 3 of 5 measures and 70 % improvement in the swollen

and tender joint count) and the DAS28 (Disease Activity Score – 28) (for information on DAS scores, see Fransen et al (2003) *Ann Rheum Dis*; 62(Suppl 1): 10; Prevoo et al. (1995) *Arthritis Rheum*; 38(1):44-48). The DAS28 is a well-established measure of disease activity in RA. The score is calculated by a complex mathematical formula, which includes the number of tender and swollen joints (out of a total of 28), the erythrocyte sedimentation rate (ESR) or hsCRP, and the patient's global assessment of global health (indicated by marking a 100 mm line between very good and very bad). A DAS28 score greater than 5.1 implies active disease, less than 3.2 well controlled disease, and less than 2.6 remission.

Example 1.3 - F2201 results

Demographics and baseline characteristics were comparable across all groups. ACR20 responders at Week 16 were higher in the secukinumab 75mg, 150mg and 300mg dose groups (46.9%, 46.5% and 53.7%, respectively) compared to placebo (36.0%) and compared to secukinumab 25mg (34%). These results did not achieve statistical significance due to a marked and unexplained increase in ACR20 in the placebo group between Week 12 (24%) and 16 (36%). Clinically relevant reductions in DAS28-CRP were observed in the secukinumab 75-300mg treatment groups vs. placebo. Serum CRP levels at Week 16 were markedly reduced in secukinumab 75-300mg groups vs. placebo ($p = 0.0012$, 0.0081 and 0.0241). ACR50 and ACR70 showed consistent greater improvements with secukinumab 75-300mg doses vs. placebo over 16 weeks. There was about a 4-fold average reduction from baseline in the HAQ[©] score at week 16 in the 150-300 mg groups compared to placebo.

By Week 24, ACR20 responses were maintained and DAS28 CRP responses further improved in the 75-300 mg groups with secukinumab treatment between week 16 and 24. The 75-300mg ACR20 responder treatment groups exhibited an early improvement in HAQ scores over time through Week 24. ACR50 responses further improved from 19 - 24% (75 mg), 21 - 25% (150mg) and 19 - 24% (300mg) in patients originally randomized to the respective dose cohort, part of whom had a dose escalation at Week 20; a similar improvement was seen in ACR70 responses in the 75 mg – 150 mg groups. An increase in the ACR20/50/70 response in the patients randomized to placebo between Week 16 and 24 was also noted.

Example 2: Materials and Method for Pharmacogenetic analysis in F2201 and A2101

In searching for markers of drug response (i.e., an RA patient's response to secukinumab), we analyzed 40 arthritis risk SNPs, multiple SNPs in IL-17A exons (15 known SNPs and 5 unreported SNPs), and genotyped patients for HLA-DRB1 alleles in efficacy data at week 12 and week 16. We additionally used data beyond week 16 to validate the association between particular HLA-DRB1 alleles and secukinumab response. Our results suggest that a high secukinumab response population exists within individuals having particular HLA-DRB1 alleles. The following discussion pertains to our analysis regarding HLA-DRB1 alleles.

Example 2.1: Samples and Processing

DNA was genotyped in 149 consenting patients who participated in the F2201 study. 121 patients who received secukinumab were used in the pharmacogenetic (PG) analysis. DNA was genotyped in 32 consenting patients who participated in the A2101 study, including 20 patients who were given 2x secukinumab 3.0 mg/kg or 2x secukinumab 10.0 mg/kg secukinumab and 12 matching placebos (FIR efficacy endpoints were only measured in these cohorts). Thirty Caucasian patients were used in the genetic analysis, including 18 on secukinumab and 12 on placebo.

Blood samples from consenting patients were collected at the individual trial sites and then shipped to Covance (Indianapolis, IN USA and Geneva, Switzerland). The genomic DNA of each patient was extracted from the blood by Covance using the PUREGENE D-50K DNA Isolation Kit (Gentra, Minneapolis, MN, USA) and shipped to Novartis for genotyping. The HLA-DRB1*SE allelic group (HLA-DRB1*01:01, 01:02, 04:01, 04:04, 04:05, 04:08, 10:01, 14:02) and the HLA-DRB1*04 allelic groups (4-digit alleles) were tested for association with differential response to secukinumab treatment. The HLA-DRB1*04 allelic group was also chosen for genotyping in A2101 to replicate the observed association with secukinumab in F2201 samples.

All samples from the F2201 study (n=150) were genotyped to sequence-specific oligonucleotide hybridization (SSO), which generally generates low resolution results for HLA alleles (2-digit allele designations). Briefly, SSO experiments were performed by using LABType® HD Class II DRB1 Typing Test (One Lambda, Inc, CA) with Luminex IS200 instrument. Data were analyzed by using HLA Fusion® 2.0 software (One Lambda). In the first and second batch of samples, one sample failed to yield results. For the remaining 149 samples,

if unambiguous at this experimental stage or ambiguities could be resolved by excluding rare alleles (see rare_alleles_2_28_0, available at bioinformatics.nmdp.org/HLA/Biannual_Rare_Allele_List/index.html), final high resolution results (4-digit allele designations) were assigned. For the samples whose genotypes were not resolved at the 4-digit level, sequence based typing (SBT) and sequence specific primer (SSP) PCR were further performed. Briefly, SBT experiments were performed by using HLA-DRB1 SBT Pack (Abbott Molecular, IL) and SBTexcellerator HLA DRB1 Kits (Qiagen, Netherlands). Sequencing products were separated on a 3730xl Genetic Analyzer (Applied Biosystems, CA) and the fluorescence of the dyes was analyzed to determine the DNA sequence. Genotype were analyzed and assigned by using SBTengine software 2.12.1.0 (Genome Diagnostics, Netherlands). SSP was performed with Olerup SSP kits (Olerup, PA). Resulting PCR amplicon were analyzed by separation on agarose gels with regard to their length by comparison with size standard. Final allelotypes were assigned by comparing to SSP worksheet provided by Olerup.

In the samples of the A2101 study (n=32), only HLA-DRB1*04 were further resolved and reported as high resolution by using methods described as above, while other allelotypes were reported as SSO data output.

Example 2.2: Statistical Analysis

Generally, statistical models for the pharmacogenetic analyses were based on the models used in the analysis of the clinical trials, adding a term for the genotype of the variant (e.g. HLA alleles) being tested and additional covariates if applicable. All variants were tested individually, i.e., only 1 variant was included in the model at a time. All HLA alleles were tested against clinical endpoints using the standard additive effect coding: individuals were coded 0, 1 or 2 for the HLA allele, depending on the number of copies of the HLA allele that an individual carries. All association tests were two-tailed, single-point tests for an additive allelic effect.

Ancestry is a common confounding factor in genetic association studies. ~87% of the 121 secukinumab-treated patients in F2201 are Caucasians. Two models were tested by race in F2201 samples: a) including all secukinumab-treated patients (N=121) and adjusting for race; b) including only Caucasian secukinumab-treated patients and not adjusting for race (N=105). Since the vast majority of the A2101 patients (~94%) are Caucasians, only the 30 Caucasian patients were eligible for the analysis in A2101.

Only secukinumab-treated patients were used for the genetic analysis in F2201 samples (N=121). The null hypothesis was that the coefficient for the genotype variable was equal to zero, and the corresponding p-value was presented. Rejecting the null hypothesis would mean concluding that genotype was a predictor of response to secukinumab as measured by the specific clinical endpoint.

Both Caucasian patients on secukinumab and on placebo were used for the genetic analysis in A2101 samples (N=30). There is an additional term included in the models in genetic analysis in A2101: the interaction between this indicator variable of treatment group and genotype variable. The null hypothesis was that the coefficient for the interaction between the treatment indicator and the genotype variable is equal to zero, and the corresponding p-value was presented. Rejecting the null hypothesis would mean concluding that the genotype is a predictor of how much better a patient is likely to respond to secukinumab than to placebo as measured by the specific clinical endpoint.

Example 2.2.1: Exploratory PG analysis in F2201

Example 2.2.1.1 DRB1 4-digit alleles in all F2201 secukinumab treated patients

Genotypes were obtained for the HLA DRB1 genes on 4-digit resolution from 149 patients in the F2201 study as described above. All DRB1 4-digit alleles were tested for association with secukinumab response.

All statistical tests were performed in SAS. Efficacy variable DAS28 derived from CRP at week 12/week 16 were analyzed separately using an ANCOVA model (SAS 9.2 PROC GLM), and efficacy variable ACR20 at week 12/week 16 were analyzed separately using a logistic regression model (SAS 9.2 PROC LOGISTIC), both with the efficacy endpoint as the dependent variable, DRB1 4-digit alleles (as coded above) as the independent variable (fixed effect), and the following fixed effect covariates:

- sex
- dosing group or drug concentration, two models tested separately
- baseline weight (included only if dosing group was adjusted for)
- race (included only if all SECUKINUMAB -treated patients were used in analysis)
- baseline DAS28 derived from CRP
- baseline RF (known to associate with efficacy response)

- baseline anti-CCP (known to associate with efficacy response)
- baseline CRP (known to associate with efficacy response)
- baseline ESR (known to associate with efficacy response)

Last observations were not carried over to impute missing values. The polymorphisms with <5% frequency in the sample were excluded.

Example 2.2.1.2 HLA-DRB1*04 alleles in all F2201 secukinumab treated patients

Similar tests were done as described above for secukinumab response at week 12/week 16, except that HLA-DRB1*04 allelic group was tested for association with secukinumab response using two-tailed, single-point tests for an additive allelic effect.

The associations between HLA-DRB1*04 allelic group and secukinumab response observed was also analyzed in data beyond week 16 in order to validate the findings at week 12/week 16. Three parts of pharmacogenetic analysis were conducted for data beyond week 16.

Part I analysis was to test for association between DRB1*04 and efficacy beyond week 16 in patients randomized to secukinumab at baseline (N=117). The ACR20 non-responders at week 20 were switched to a higher dose of secukinumab, which may lead to loss of power in this analysis. Part II analysis was done in secukinumab-treated patients defined as ACR20 responders at week 16 (N=54). This analysis should not be affected by potential confounding due to changes in dosing regimen since this subgroup remained at original dosing. Part III analysis was done in the placebo arm. The placebo group was switched to secukinumab 150 mg at week 20. So week 20 is used as the baseline in this analysis.

Example 2.2.1.3 HLA-DRB1*04 alleles in F2201 secukinumab treated patients not treated with anti-TNF before

Similar tests were done as described above, except that the patients previously treated with anti-TNF were excluded.

Example 2.2.1.4 HLA-DRB1*SE alleles in all F2201 secukinumab treated patients

Similar tests were done as described above, except that DRB1 SE allelic group (HLA-DRB1*01:01, 01:02, 04:01, 04:04, 04:05, 04:08, 10:01, 14:02) was tested for association with secukinumab response using two-tailed, single-point tests for an additive allelic effect.

Example 2.2.2: Test the association between HLA-DRB1*04 and secukinumab response in A2101**Example 2.2.2.1 Primary Objective - Test the effect of HLA-DRB1*04 on DAS28 (interaction term) on Day 43 (week 6)**

Genotypes were obtained for the HLA DRB1 genes on 2-digit resolution from the 32 consented patients in the A2101 study as described above. The allelic group HLA-DRB1*04 was tested for association by comparing patients carrying at least one HLA-DRB1*04 allele (coded as 1) to patients not carrying this allele (coded as 0) and determining whether secukinumab response differed significantly between these two groups. The dominant genetic model was used in this test since there was only one patient carrying two HLA-DRB1*04 alleles in this small sample. Both secukinumab-treated patients and patients on placebo were used for the genetic analysis in A2101 samples.

The statistical test was performed in SAS. The efficacy variable used in this test is the change of DAS28 at day 43 from baseline (blinded observer's assessment). The efficacy variable was analyzed using an ANCOVA model (SAS 9.2 PROC GLM), with the efficacy endpoint as the dependent variable, the genotype variable of HLA-DRB1*04 carrying status (coded as above) as the independent variable (fixed effect), treatment group (an indicator of whether the patient was randomized to receive secukinumab or placebo) and baseline DAS28 as fixed effect covariates, and an additional included in the model: the interaction between this indicator variable of treatment group and genotype variable.

Example 2.2.2.2 Secondary Objectives**Test the effect of HLA-DRB1*04 on ACR20/ACR50 (interaction term) on Day 43 (week 6)**

The similar tests were done as described above, except that ACR20/ACR50 on Day 43 (week 6) were used as the efficacy variables. The two efficacy variables were analyzed separately using logistic regression models (SAS 9.2 PROC LOGISTIC).

Test the effect of HLA-DRB1*04 on DAS28/ACR20/ACR50 (interaction term) over repeated visits (week 3, 4, 5, 6)

The effects of HLA-DRB1*04 on the efficacy endpoints DAS28/ACR20/ACR50 (interaction term) over repeated visits (week 3, 4, 5, 6) were analyzed using a generalized estimation equation (GEE) method (SAS 9.2 PROC GENMOD) to account for correlation between repeated measures. The model has the efficacy endpoint as the dependent variable, HLA-DRB1*04 alleles as the independent variable (fixed effect), treatment group (an indicator of whether the patient was randomized to receive secukinumab or placebo) and baseline DAS28 as fixed effect covariates, and an additional included in the model: the interaction between this indicator variable of treatment group and the genotype variable. The estimated structure on the correlation between the outcomes at different times was auto-regressive (TYPE=AR in SAS 9.2 PROC GENMOD).

Example 3: Results for Pharmacogenetic analysis in F2201 (Week 12 and 16)**Example 3.1 Exploratory PG analysis in F2201****Example 3.1.1 Test the effect of HLA-DRB1 alleles on secukinumab response****Example 3.1.1.1 Effect of HLA-DRB1 alleles on secukinumab response in all F2201 secukinumab-treated patients**

Among the 4-digit DRB1 alleles, HLA-DRB1*0401 has the best p value, with nominal $p=0.0394$ for association with ACR20 at week 12 in all 121 patients using an additive model adjusting for drug concentration, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline anti-CCP, baseline CRP and baseline ESR.

Example 3.1.1.2 Effect of HLA-DRB1*04 alleles on secukinumab response in all F2201 secukinumab-treated patients

48% Patients in the 121 secukinumab-treated patients in F2201 have at least one HLA-DRB1*04 allele. As shown in **Table 5**, a higher percentage of patients having at least one HLA-DRB1*04 allele achieve ACR20 and ACR50 at both week 12 and 16 following treatment with secukinumab.

The following results were obtained:

- p value = 0.0032, odds ratio (OR) = 2.78 for association with ACR20 at week 12 in all 121 patients using additive model adjusting for drug concentration, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline anti-CCP, baseline CRP and baseline ESR.
- p value = 0.0046, beta = - 0.49 for association with DAS28 at week 16 in all 121 patients using additive model adjusting for drug concentration, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline anti-CCP, baseline CRP and baseline ESR.
- p value = 0.0082, beta = - 0.43 for association with DAS28 at week 12 in all 121 patients using additive model adjusting for drug concentration, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline antiCCP, baseline CRP and baseline ESR.

Percent patients reaching endpoint in secukinumab arm	Week	HLA-DRB1*04 + (n=59)	HLA-DRB1*04 – (n=62)	All patients (n=121)
% reaching ACR20	week 12	63.8	39.3	51.2
	week 16	52.6	42.3	47.4
% reaching ACR50	week 12	15.5	8.2	11.8
	week 16	21.1	10.2	15.6
% reaching ACR70	week 12	1.7	0	0.84
	week 16	3.5	5.1	4.27

Table 5 shows the percent of secukinumab-treated patients reaching a given endpoint (ACR20, ACR50, ACR70). HLA-DRB1*04 – = patients with no HLA-DRB1*04 allele; HLA-DRB1*04 + = patients with at least one HLA-DRB1*04 allele.

The effect of HLA-DRB1*04 alleles on response to treatment with secukinumab may also be seen in **Figure 1**. At week 12, homozygous individuals (those carrying two copies of HLA-DRB1*04 alleles) have the highest ACR20 response rate, followed by heterozygous individuals (those carrying one copy of HLA-DRB1*04 allele). Similar results are seen in

Figure 2, which shows the additive effect of HLA-DRB1*04 alleles on the percent of secukinumab-treated patients reaching ACR50 at week 12 and 16. At week 12 and 16, homozygous HLA-DRB1*04 individuals have the highest ACR50 response rate, followed by heterozygous individuals. A similar impact may be seen on DAS28 scores at weeks 12 and 16 (**Figure 3**), which shows the additive effect of HLA-DRB1*04 alleles on the DAS28 score of secukinumab-treated patients. At weeks 12 and 16, HLA-DRB1*04 homozygous individuals have the lowest DAS28 score, followed by heterozygous individuals.

As shown in **Table 6**, HLA-DRB1*04 alleles associate with a larger decrease in DAS28 (indicating an increased response) at week 12 and week 16 in secukinumab-treated patients across all doses and a decreased response in the placebo arm (MTX). Further, HLA-DRB1*04 alleles associate with an increased percentage reaching ACR20 at Week 12 in secukinumab-treated patients across all doses and a decreased response in the placebo arm (MTX).

Treatment (mg secukinumab)	N	DAS28_CRP Week 12 (change in score)	DAS28_CRP Week 16 (change in score)	ACR20 Week 12 (% achieving)	ACR20 Week 16 (% achieving)	ACR50 Week 12 (% achieving)	ACR50 Week 16 (% achieving)
HLA-DRB1*04 allele carrier							
0 mg (Placebo)	13	-0.45	-0.06	8.33	25.00	0.00	0.00
25 mg	15	-1.36	-1.47	60.00	42.86	0.00	14.29
75 mg	19	-1.70	-1.95	66.67	50.00	33.33	33.33
150 mg	15	-1.61	-1.84	66.67	66.67	13.33	20.00
300 mg	10	-1.62	-1.75	60.00	50.00	10.00	10.00
HLA-DRB1*04 allele non-carrier							
0 mg (Placebo)	15	-0.94	-1.40	28.57	28.57	0.00	7.14
25 mg	19	-0.96	-0.86	26.32	33.33	5.26	11.11
75 mg	13	-1.15	-1.08	38.46	50.00	7.69	0.00
150 mg	12	-0.74	-0.55	50.00	25.00	8.33	8.33
300 mg	18	-1.02	-1.22	47.06	58.82	11.76	17.65

Table 6 shows the DAS28_CRP score change and percent of patients reaching ACR20 or ACR50 at week 12 and week 16 by carrier/non-carrier status and treatment (placebo, 25 mg, 75 mg, 150 mg or 300 mg secukinumab) in all patients.

Example 3.1.1.3 effect of HLA-DRB1*04 alleles on secukinumab response in F2201 secukinumab-treated patients not previously treated with anti-TNF

A total of 15% of qualified F2201 patients were previously treated with anti-TNF therapy. To test if patients with poor response to anti-TNF therapy (refractory) are refractory to treatment with secukinumab, analysis similar to that above was conducted by excluding the patients who were previously treated with anti-TNF therapy. As shown in **Table 7**, similar association between HLA-DRB1*04 and secukinumab response was observed in the no-anti-TNF subgroup as in all patients.

Treatment (mg secukinumab)	N	DAS28_CRP Week 12 (change in score)	DAS28_CRP Week 16 (change in score)	ACR20 Week 12 (% achieving)	ACR20 Week 16 (% achieving)	ACR50 Week 12 (% achieving)	ACR50 Week 16 (% achieving)
HLA-DRB1*04 allele carrier							
0 mg (Placebo)	11	-0.61	-0.28	10.00	30.00	0.00	0.00
25 mg	13	-1.45	-1.45	61.54	38.46	0.00	7.69
75 mg	18	-1.60	-1.88	64.71	47.06	29.41	29.41
150 mg	12	-1.66	-1.78	66.67	66.67	0.00	16.67
300 mg	7	-2.08	-1.88	85.71	57.14	14.29	0.00
HLA-DRB1*04 allele non-carrier							
0 mg (Placebo)	13	-1.00	-1.36	33.33	25.00	0.00	8.33
25 mg	15	-1.05	-0.94	33.33	35.71	6.67	14.29
75 mg	10	-1.29	-1.34	40.00	50.00	0.00	0.00
150 mg	12	-0.74	-0.55	50.00	25.00	8.33	8.33
300 mg	16	-1.05	-1.23	53.33	66.67	13.33	20.00

Table 7 shows the DAS28_CRP score change and percent of patients reaching ACR20, or ACR50 at week 12 and week 16 by carrier/non-carrier and treatment (placebo, 25 mg, 75 mg, 150 mg or 300 mg secukinumab) in patients who had not previously been treated with secukinumab.

Example 3.1.1.4 Effect of HLA-DRB1*SE alleles on secukinumab response in F2201 secukinumab-treated patients

As shown in **Table 8**, a higher percentage of patients having at least one HLA-DRB1*SE allele achieve ACR20, ACR50 and ACR70 at both week 12 and 16 following treatment with secukinumab.

The following results were obtained:

- p value = 0.010, OR=3.92 for association with ACR50 at week 12 in all 121 patients using additive model adjusting for drug concentration, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline anti-CCP, baseline CRP and baseline ESR.

- p value = 0.027, OR=13.31 for association with ACR50 at week 12 in all 121 patients using dominant model adjusting for drug concentration, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline anti-CCP, baseline CRP and baseline ESR.
- p value = 0.025, beta= - 0.57 for association with DAS28 at week 16 in all 121 patients using dominant model adjusting for drug concentration, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline anti-CCP, baseline CRP and baseline ESR.

Percent patients reaching endpoint in secukinumab arm	Week	HLA-DRB1*SE + (n=78)	HLA-DRB1*SE – (n=43)	All Patients (n=121)
% reaching ACR20	week 12	54.6	45.2	51.3
	week 16	50.7	40.0	47.0
% reaching ACR50	week 12	16.9	2.4	11.8
	week 16	18.2	10.0	15.4
% reaching ACR70	week 12	1.3	0	0.8
	week 16	6.5	0	4.3

Table 8 shows the percent of secukinumab-treated patients reaching a given endpoint (ACR20, ACR50, ACR70). DRB1*SE – = patients with no HLA-DRB1*SE allele; HLA-DRB1*SE + = patients with at least one HLA-DRB1*SE allele.

As shown in **Table 9**, HLA-DRB1*SE alleles associate with a larger decrease in DAS28 at week 12 and week 16 in secukinumab-treated patients in the 150 mg and 300 mg dose arms and a decreased response in the placebo arm (MTX). HLA-DRB1*SE alleles associate with an increased percentage reaching ACR20 at Week 12 and 16 in secukinumab-treated patients in the 75 mg – 300 mg arms and a decreased response in the placebo arm (MTX). HLA-DRB1*SE alleles also associated with an increased percentage reaching ACR50 at Week 12 and 16 in secukinumab-treated patients in the 75 mg – 300 mg arms at week 16.

Treatment (mg secukinumab)	N	DAS28_CRP Week 12 (change in score)	DAS28_CRP Week 16 (change in score)	ACR20 Week 12 (% achieving)	ACR20 Week 16 (% achieving)	ACR50 Week 12 (% achieving)	ACR50 Week 16 (% achieving)
HLA-DRB1*SE allele carrier							
0 mg (Placebo)	20	-0.66	-0.58	11.11	22.22	0.00	0.00
25 mg	25	-1.13	-1.23	40.00	36.00	4.00	12.00
75 mg	20	-1.46	-1.59	57.89	52.63	31.58	26.32
150 mg	16	-1.65	-1.72	68.75	62.50	18.75	18.75

300 mg	17	-1.56	-1.77	58.82	58.82	17.65	17.65
HLA-DRB1*SE allele non-carrier							
0 mg (Placebo)	8	-0.88	-1.19	37.50	37.50	0.00	12.50
25 mg	9	-1.14	-0.70	44.44	37.50	0.00	12.50
75 mg	12	-1.52	-1.63	50.00	45.45	8.33	9.09
150 mg	11	-0.61	-0.62	45.45	27.27	0.00	9.09
300 mg	11	-0.70	-0.82	40.00	50.00	0.00	10.00

Table 9 shows the DAS28_CRP score change and percent of patients reaching ACR20 or ACR50 at week 12 and week 16 by HLA-DRB1*SE allele carrier/non-carrier status and treatment (placebo, 25 mg, 75 mg, 150 mg or 300 mg secukinumab) in all patients.

Example 4: Analysis of HLA-DRB1*04 Alleles in A2101 Study (Week 7)

Example 4.1 Primary objective results

HLA-DRB1*04 allele carrier/non-carrier status significantly associates with secukinumab response, with $p = 0.042$ for the interaction term HLA-DRB1*04 x Treatment after permutation, using Blinded Observer's Assessment of DAS28 on Day 43 as the efficacy measurement. As shown in Table 10, HLA-DRB1*04 carrier/non-carrier status also identifies a subgroup with better response to secukinumab than to Placebo (MTX) using Blinded Observer's Assessment of DAS28 on Day 43 as the efficacy measurement. Furthermore, HLA-DRB1*04 alleles associate with increased response in secukinumab arm and decreased response in placebo arm (MTX) using Investigator's Assessment of DAS28 on Day 43 as the efficacy measurement.

Treatment	N	DAS28_CRP at day 43 Blinded Observer's Assessment (change in score)	DAS28_CRP at day 43 Investigator's Assessment (change in score)	ACR20 at day 43 Blinded Observer's Assessment (% achieving)	ACR20 at day 43 Investigator's Assessment (% achieving)	ACR50 at day 43 Blinded Observer's Assessment (% achieving)	ACR50 at day 43 Investigator's Assessment (% achieving)
HLA-DRB1*04 allele carrier							
Placebo	7	-0.71	-0.87	14.29	14.29	0.00	0.00
secukinumab	10	-1.54	-1.78	50.00	60.00	30.00	30.00
HLA-DRB1*04 allele non-carrier							
Placebo	5	-2.61	-1.79	40.00	60.00	20.00	40.00
secukinumab	8	-1.38	-1.06	25.00	25.00	12.50	12.50

Table 10 shows the DAS28_CRP score change and percent of patients reaching ACR20 or ACR50 at day 43 by HLA-DRB1*04 allele carrier/non-carrier status and treatment (placebo or secukinumab) in all Caucasian patients.

Example 4.2 Secondary objective results

As shown in **Table 11**, HLA-DRB1*04+ subgroup has higher % reaching ACR20/ACR50 in secukinumab-treated patients. The genotype*treatment interaction term is not statistically significant for ACR20/ACR50 on Day 43, most likely due to lack of power when using binary efficacy endpoints. However, significant genotype*treatment interaction was observed for ACR20 using GEE method to account for correlation between repeated measures (week 3, 4, 5, 6), with $p = 0.025$. The effect of HLA-DRB1*04 on DAS28, ACR20 and ACR50 response is sustained over time in the A2101 sample.

Percent patients reaching endpoint in secukinumab arm (Caucasian only)	Week	HLA-DRB1*04 + (n=10)	HLA-DRB1*04 – (n=8)	All Patients (n=18)
% reaching ACR20 (Investigator's Assessment)	Week 5	60.0	37.5	50.0
	Week 6	50.0	25.0	38.9
% reaching ACR50 (Investigator's Assessment)	Week 5	40.0	0	22.2
	Week 6	30.0	12.5	22.2

Table 11 shows the percent of secukinumab-treated patients reaching a given endpoint (ACR20, ACR50, ACR70). HLA-DRB1*04– = patients with no HLA-DRB1*04 allele; HLA-DRB1*04 + = patients with at least one HLA-DRB1*04 allele.

Example 5: Results for Pharmacogenetic Analysis in F2201 Beyond Week 16

Example 5.1: Analysis of All Patients Randomized to Secukinumab at Baseline

We tested for association between HLA-DRB1*04 and efficacy beyond week 16 in patients randomized to secukinumab at baseline (N=117). It was observed that HLA-DRB1*04 associates with better secukinumab response in ACR50 (**Figure 4**), ACR20 (**Figure 5**) and DAS28 score (**Figure 6**) over time.

The following results were obtained:

- $P=0.0057$, odds ratio (OR) = 3.97 for association with ACR50 at week 52 in the 117 patients randomized to secukinumab at baseline using additive model adjusting for dosing groups, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline anti-CCP, baseline CRP and baseline ESR.

- p value = 0.0023, beta = -0.60 for association with DAS28 at week 52 in the 117 patients randomized to secukinumab at baseline using additive model adjusting for dosing groups, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline anti-CCP, baseline CRP and baseline ESR.

As shown in **Table 12**, HLA-DRB1*04 alleles associate with a larger decrease in DAS28 (indicating an increased response) at week 52 in secukinumab-treated patients across all doses except the 25 mg dose. Further, HLA-DRB1*04 alleles associate with an increased percentage reaching ACR50 at Week 52 in secukinumab-treated patients across all doses. Similar findings were observed in the subgroup analysis of anti-TNF naive patients. Data beyond week 16 support the association between DRB1*04 and response observed in week 12 and week 16 data. As a caveat, the ACR20 non-responders at week 20 were switched to a higher dose of secukinumab, which may lead to loss of power in this analysis.

Treatment	ACR50 (% achieving)	DAS28 CRP (decrease from baseline)
Carrier*04 alleles		
25 mg	28.57 (n=7)	0.99 (n=7)
75 mg	60.00 (n=10)	2.44 (n=10)
150 mg	20.00 (n=25)	1.78 (n=24)
300 mg	14.29 (n=14)	1.37 (n=13)
Non-carrier *04 alleles		
25 mg	0 (n=7)	2.02 (n=6)
75 mg	0 (n=7)	0.70 (n=7)
150 mg	5.56 (n=18)	1.20 (n=18)
300 mg	11.11 (n=27)	1.15 (n=27)

Table 12: Week 52 results for all secukinumab patients in study F2201.

Example 5.2: Subgroup Analysis of Secukinumab-Treated Patients Defined as ACR20 Responders at Week 16

This subgroup analysis was done in secukinumab-treated patients defined as ACR20 responders at week 16. The goal of this analysis was to test for association between DRB1*04 and efficacy beyond week 16 in secukinumab-treated patients defined as ACR20 responders at week 16 (N=54). This analysis should not be affected by potential confounding due to changes in dosing regimen since this subgroup remained at original dosing. It was observed that HLA-

DRB1*04 associates with better secukinumab response in ACR50 (**Figure 7**), ACR20 (**Figure 8**) and DAS28 score (**Figure 9**) over time.

The following results were obtained:

- $p=0.0082$, odds ratio (OR) = 70.81 for association with ACR50 at week 52 in the 54 patients defined as ACR20 responders at week 16 using additive model adjusting for dosing groups, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline anti-CCP, baseline CRP and baseline ESR.
- p value = 0.013, β = -0.81 for association with DAS28 at week 52 in the 54 patients defined as ACR20 responders at week 16 using additive model adjusting for dosing groups, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline anti-CCP, baseline CRP and baseline ESR.

As shown in **Table 13**, HLA-DRB1*04 alleles associate with a larger decrease in DAS28 (indicating an increased response) at week 52 in secukinumab-treated patients defined as ACR20 responders at week 16 across all doses except the 25 mg dose. Further, HLA-DRB1*04 alleles associate with an increased percentage reaching ACR50 at Week 52 in secukinumab-treated patients across all doses. Similar findings were observed in the subgroup analysis of anti-TNF naive patients. This genetic analysis supports the association between DRB1*04 and response observed in week 12 and week 16 data.

Treatment	ACR50 (% achieving)	DAS28_CRP (change from baseline)
Carrier *04 alleles		
25 mg	33.33 (n=6)	1.27 (n=6)
75 mg	66.67 (n=9)	2.74 (n=9)
150 mg	50.00 (n=10)	2.60 (n=9)
300 mg	50.00 (n=4)	3.07 (n=3)
Non-carrier *04 alleles		
25 mg	0 (n=6)	2.40 (n=5)
75 mg	0 (n=6)	0.90 (n=6)
150 mg	0 (n=3)	1.85 (n=3)
300 mg	30.00 (n=10)	1.84 (n=10)

Table 13: Week 52 results for subgroup analysis of secukinumab-treated patients defined as ACR20 responders at week 16

Example 5.3 Subgroup Analysis of Placebo Arm (Switched to 150 mg Secukinumab at Week 20)

This subgroup analysis was done in the placebo arm. The placebo group was switched to secukinumab 150 mg at week 20. Data at week 20 are not available. As a result, week 16 is used as the baseline in this analysis. The goal of this analysis was to replicate the association between DRB1*04 and response observed in secukinumab arm in an independent sample.

The following results were obtained:

In the full placebo group (N=25, **Table 14**):

- $p=0.30$, odds ratio (OR) = 11.59 for association with ACR50 at week 52 in the full placebo group (N=25) using additive model adjusting for race and baseline DAS28 derived from CRP (additional covariates were dropped so that the model may converge).
- p value = 0.92, $\beta = -0.053$ for association with DAS28 at week 52 in the 54 patients defined as ACR20 responders at week 16 using additive model adjusting for dosing groups, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline anti-CCP, baseline CRP and baseline ESR.

In the placebo group not treated with anti-TNF before (N=20, **Table 14**):

- Only 2 patients reached ACR50 in this subgroup and thus p value was not calculated for association with ACR50.
- p value = 0.47, $\beta = -0.53$ for association with DAS28 at week 52 in the 54 patients defined as ACR20 responders at week 16 using additive model adjusting for dosing groups, sex, race, baseline DAS28 derived from CRP, baseline RF, baseline anti-CCP, baseline CRP and baseline ESR.

In the full placebo group (N=25), there was no consistent evidence of association with response to secukinumab in ACR50 (**Figure 10**) or ACR 20 (**Figures 11**). While the mean reduction of DAS28 score from week 16 to week 52 was higher in the HLA-DRB1*04 carriers (**Figure 12**), this trend of association seems to mainly arise from baseline confounding factors. It is unclear why the association between HLA-DRB1*04 and secukinumab response was not replicated in the full placebo arm subgroup analysis. However, the sample size is very small for the purpose of replication. Furthermore, at week 20 the placebo arm was switched from placebo

(MTX) to secukinumab 150 mg. These factors, together with the unexpectedly high placebo effect observed in the clinical study at week 16, may bring bias to the subgroup analysis of Example 5.3.

Interestingly, the trend of association in anti-TNF naive patients subgroup (N=20) was generally consistent with that in the secukinumab arm (p value not significant). It was observed that HLA-DRB1*04 associates with better secukinumab response (**Figure 13-15**) in the anti-TNF naive patients over time. While the placebo arm subgroup did not show association between HLA-DRB1*04 and secukinumab response, a subgroup of this subgroup (i.e., anti-TNF naive patients) did show a trend of association, which could mean that there is a particular value in using secukinumab in anti-TNF naive patients. However, the small sample size employed in Example 5.3 (N=25 for full placebo group; N=20 for anti-TNF naive placebo group), necessitates caution when interpreting any data in these groups.

Treatment	ACR50 (% achieving)	DAS28_CRP (change from week 16)
Carrier *04 alleles		
All Patients	9.09 (n=11)	1.08 (n=11)
Anti-TNF naive	10.00 (n=10)	1.22 (n=10)
Non-carrier*04 alleles		
All Patients	21.43 (n=14)	0.62 (n=12)
Anti-TNF naive	10.00 (n=10)	0.89 (n=8)

Table 14: Week 52 results for subgroup analysis of placebo arm (switched to 150 mg secukinumab at week 20).

In conclusion, the data provided herein supports an association between HLA-DRB1*04 and/or HLA-DRB1*SE status and RA patient's response to secukinumab, as measured by DAS28 and ACR scores. This finding is currently undergoing validation in prospective clinical trials. Notably, it has been previously shown that the SE does not predict response to biological agents, particularly to anti-TNF factor treatments such as etanercept and infliximab (Potter et al. (2009) Ann. Rheum. Dis. 68:69-74). Potter et al showed that there was no association between anti-TNF response and carriage of risk alleles for either of the two well established RA susceptibility factors, SE or *PTPN22*. As such, our determination that there is a significant association between HLA-DRB1*04 and/or HLA-DRB1*SE status and RA patient's response to secukinumab is surprising.

WHAT IS CLAIMED IS:

1. A method of predicting the likelihood that a patient having rheumatoid arthritis (RA) will respond to treatment with an IL-17 antagonist, comprising assaying a biological sample from the patient for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group, wherein the presence of the at least one allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the at least one allele is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.
2. A method of predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist, comprising:
 - a) obtaining a biological sample from said patient; and
 - b) assaying the biological sample for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group, wherein the presence of the at least one allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the at least one allele is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.
3. The method according to any one of claims 1-2, wherein the presence of two alleles in the HLA-DRB1*04 allelic group in the biological sample is indicative of a further increased likelihood that the patient will respond to treatment with the IL-17 antagonist.
4. A method of predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist, comprising assaying a biological sample from the patient for the presence or absence of a shared epitope (SE), wherein the presence of the SE is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the SE is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.
5. A method of predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist, comprising:

- a) obtaining a biological sample from said patient; and
- b) assaying the biological sample for the presence or absence of a SE, wherein the presence of the SE is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the SE is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 IL-17 antagonist.

6. The method according to any one of claims 4-5, wherein the presence or absence of the SE is detected by assaying the biological sample for the presence or absence of at least one allele in the HLA-DRB1*SE allelic group.

7. The method according to claim 6, wherein the presence of two alleles in the HLA-DRB1*SE allelic group in the biological sample is indicative of a further increased likelihood that the patient will respond to treatment with the IL-17 antagonist.

8. The method according to any one of claims 1-3 or 6-7, wherein the presence or absence of the at least one allele is detected by assaying the biological sample for a genomic sequence of the at least one allele, a product of the at least one allele, or an equivalent genetic marker of the at least one allele.

9. Use of at least one probe capable of detecting the presence of at least one allele in the HLA-DRB1*04 allelic group in a biological sample from a patient having RA for predicting the likelihood that the patient will respond to treatment with an IL-17 antagonist, wherein the presence of the at least one allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the at least one allele is indicative of a decreased likelihood likelihood that the patient will respond to treatment with the IL-17 antagonist.

10. The use according to claim 9, wherein the presence of two alleles in the HLA-DRB1*04 allelic group in the biological sample is indicative of a further increased likelihood that the patient will respond to treatment with the IL-17 antagonist.

11. Use of at least one probe capable of detecting the presence of a SE in a biological sample from a patient having RA for predicting the likelihood that the patient will respond to treatment

with an IL-17 antagonist, wherein the presence of the at least one allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the at least one allele is indicative of a decreased likelihood likelihood that the patient will respond to treatment with the IL IL-17 antagonist.

12. The use according to claim 11, wherein the presence of the SE is detected by assaying the biological sample for the presence of at least one allele in the HLA-DRB1*SE allelic group.

13. The use according to claim 12, wherein the presence of two alleles in the HLA-DRB1*SE allelic group in the biological sample is indicative of a further increased likelihood that the patient will respond to treatment with the IL-17 antagonist.

14. The use according to any one of claims 9-10 or 12-13, wherein the presence or absence of the at least one allele is detected by assaying the biological sample for a genomic sequence of the at least one allele, a product of the at least one allele, or an equivalent genetic marker of the at least one allele.

15. A kit for use in predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist comprising,

a) at least one probe capable of detecting the presence of at least one allele in the HLA-DRB1*04 allelic group; and

b) instructions for using the probe to assay a biological sample from the RA patient for the presence of the at least one allele, wherein the presence of the at least one allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the at least one allele is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.

16. A kit for use in treating a patient having RA comprising,

a) a therapeutically effective amount of an IL-17 antagonist;

b) at least one probe capable of detecting the presence of at least one allele in the HLA-DRB1*04 allelic group;

c) instructions for using the probe to assay a biological sample from the patient for the presence of the at least one allele,

- d) instructions for administering the IL-17 antagonist to the patient if the biological sample from the patient has the presence of the at least one allele;
 - e) optionally, means for administering the IL-17 antagonist to the patient;
- and
- f) optionally, a therapeutically effective amount of at least one anti-rheumatic agent selected from the group consisting of an immunosuppressive agent, a disease-modifying anti-rheumatic drug (DMARD), a pain-control drug, a steroid, a non-steroidal anti-inflammatory drug (NSAID), a cytokine antagonist, a bone anabolic, a bone anti-resorptive, and combinations thereof.

17. A kit for use in predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist comprising,

- a) at least one probe capable of detecting the presence of a SE; and
- b) instructions for using the probe to assay a biological sample from the RA patient for the presence or absence of the SE, wherein the presence of the SE is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the SE is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.

18. A kit for use in treating a patient having RA comprising,

- a) a therapeutically effective amount of an IL-17 antagonist;
 - b) at least one probe capable of detecting the presence of a SE;
 - c) instructions for using the probe to assay a biological sample from the patient for the presence or absence of the SE,
 - d) instructions for administering the IL-17 antagonist to the patient if the biological sample from the patient has the presence of the SE;
 - e) optionally, means for administering the IL-17 antagonist to the patient;
- and
- f) optionally, a therapeutically effective amount of at least one anti-rheumatic agent selected from the group consisting of an immunosuppressive agent, a disease-modifying anti-rheumatic drug (DMARD), a pain-control drug, a steroid, a non-steroidal anti-

inflammatory drug (NSAID), a cytokine antagonist, a bone anabolic, a bone anti-resorptive, and combinations thereof.

19. The kit according to any one of claims 17-18, wherein the probe is capable of detecting the presence of at least one allele in the HLA-DRB1*SE allelic group.

20. The kit according to any one of claims 15-16 or 19, wherein the probe is an oligonucleotide that specifically hybridizes to a region of a nucleic acid coding for the at least one allele, an antibody that detects a polypeptide product of the at least one allele, or an oligonucleotide that specifically hybridizes to a region of a nucleic acid coding for an equivalent genetic marker of the at least one allele.

21. Use of a kit comprising at least one probe capable of detecting at least one allele in the HLA-DRB1*04 allelic group for predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist.

22. Use of a kit comprising at least one probe capable of detecting a SE for predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist.

23. The use according to claim 22, wherein the probe is capable of detecting the presence of at least one allele in the HLA-DRB1*SE allelic group.

24. The use according to any one of claims 21 or 23, wherein the probe is an oligonucleotide that specifically hybridizes to a region of a nucleic acid coding for the at least one allele, an antibody that detects a polypeptide product of the at least one allele, or an oligonucleotide that specifically hybridizes to a region of a nucleic acid coding for an equivalent genetic marker of the at least one allele.

25. A method of treating RA, comprising
a) obtaining a biological sample from an RA patient; and
b) assaying the biological sample for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and

- c) administering a therapeutically effective amount of an IL-17 antagonist to the RA patient if the biological sample has the presence of the at least one allele.
26. A method of treating RA, comprising:
- a) assaying a biological sample from an RA patient for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and
 - b) administering a therapeutically effective amount of an IL-17 antagonist to the RA patient if the biological sample has the presence of the at least one allele.
27. A method of selectively treating a patient having RA, comprising:
- a) determining whether a biological sample from the patient has the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and
 - b) administering a therapeutically effective amount of an IL-17 antagonist to the RA patient if the biological sample has the presence of the at least one allele.
28. A method of treating an RA patient, comprising:
- a) receiving data regarding the presence or absence in a biological sample obtained from said patient of at least one allele in the HLA-DRB1*04 allelic group; and
 - b) administering an IL-17 antagonist to the patient if said received data indicates that the patient has the at least one allele.
29. A method of treating RA, comprising:
- a) obtaining a biological sample from an RA patient; and
 - b) assaying the biological sample for the presence or absence of a SE; and
 - c) administering a therapeutically effective amount of an IL-17 antagonist to the RA patient if the biological sample has the presence of the SE.
30. A method of treating RA, comprising
- a) assaying a biological sample from an RA patient for the presence or absence of a SE; and
- and
- b) administering a therapeutically effective amount of an IL-17 antagonist to the RA patient if the biological sample has the presence of the SE.

31. A method of selectively treating a patient having RA, comprising
- a) determining whether a biological sample from the patient has the presence or absence of a SE; and
 - b) administering a therapeutically effective amount of an IL-17 antagonist to the RA patient if the biological sample has the presence of the SE.
32. A method of treating an RA patient comprising:
- a) receiving data regarding the presence or absence in a biological sample obtained from said patient of a SE; and
 - b) administering an IL-17 antagonist to the patient if said received data indicates that the patient has the at least one allele.
33. The method according to any one of claims 29-32, wherein the presence or absence of the SE is detected by assaying the biological sample for the presence or absence of at least one allele in the HLA-DRB1*SE allelic group.
34. The method according to any one of claims 25-28 or 33, wherein the presence or absence of the at least one allele is detected by assaying the biological sample for a genomic sequence of the at least one allele, a product of the at least one allele, or an equivalent genetic marker of the at least one allele.
35. A method of treating RA, comprising
- a) selecting an RA patient for treatment on the basis of the RA patient having at least one allele in the HLA-DRB1*04 allelic group; and
 - b) administering a therapeutically effective amount of an IL-17 antagonist to the RA patient.
36. A method of treating RA, comprising administering an IL-17 antagonist to an RA patient that has an increased likelihood of responding to said IL-17 antagonist, wherein said increased likelihood is determined on the basis of the patient having at least one allele in the HLA-DRB1*04 allelic group.

37. A method of treating RA, comprising administering an IL-17 antagonist to an RA patient that has an increased likelihood of responding to said IL-17 antagonist, wherein said increased likelihood is identified by the method set forth in claim 1.
38. A method of treating RA, comprising administering a therapeutically effective amount of an IL-17 antagonist to an RA patient, provided that the RA patient has at least one allele in the HLA-DRB1*04 allelic group.
39. A method of treating RA, comprising
- a) selecting an RA patient for treatment on the basis of the RA patient having a SE; and
 - b) administering a therapeutically effective amount of an IL-17 antagonist to the RA patient.
40. A method of treating RA, comprising administering an IL-17 antagonist to an RA patient that has an increased likelihood of responding to said IL-17 antagonist, wherein said increased likelihood is determined on the basis of the patient having a SE.
41. A method of treating RA, comprising administering an IL-17 antagonist to an RA patient that has an increased likelihood of responding to said IL-17 antagonist, wherein said increased likelihood is identified by the method set forth in claim 4.
42. A method of treating RA, comprising administering a therapeutically effective amount of an IL-17 antagonist to an RA patient, provided that the RA patient has a SE.
43. The method according to any one of claims 25-42, wherein the step of administering comprises intravenously administering three doses of about 10 mg/kg of the IL-17 antagonist to said patient, each of said doses being administered every other week
44. The method according to any one of claims 25-42, wherein the step of administering comprises subcutaneously administering the patient about 75 mg - about 300 mg of the IL-17 antagonist twice a month, monthly, every two months or every three months.
45. An IL-17 antagonist for use in treating RA, characterized in that:
- a) a biological sample is obtained from an RA patient

b) the biological sample is assayed for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and

c) a therapeutically effective amount of an IL-17 antagonist is administered to the RA patient if the biological sample has the presence of the at least one allele.

46. An IL-17 binding molecule for use in treating RA, characterized in that:

a) a biological sample from an RA patient is assayed for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and

b) a therapeutically effective amount of an IL-17 antagonist is administered to the RA patient if the biological sample has the presence of the at least one allele.

47. An IL-17 binding molecule for use in treating RA, characterized in that:

a) a biological sample is obtained from an RA patient

b) the biological sample is assayed for the presence or absence of a SE; and

c) a therapeutically effective amount of an IL-17 antagonist is administered to the RA patient if the biological sample has the presence of the at least one allele.

48. An IL-17 binding molecule for use in treating RA, characterized in that:

a) a biological sample from an RA patient is assayed for the presence or absence of the SE; and

b) a therapeutically effective amount of an IL-17 antagonist is administered to the RA patient if the biological sample has the presence of the at least one allele.

49. The use according to any one of claims 47-48, wherein the presence or absence of the SE is detected by assaying the biological sample for the presence or absence of at least one allele in the HLA-DRB1*SE allelic group.

50. The use according to any one of claims 45-46 or 49, wherein the presence or absence of the at least one allele is detected by assaying the biological sample for a genomic sequence of the at least one allele, for a product of the at least one allele, or for an equivalent genetic marker of the at least one allele.

51. An IL-17 binding molecule for use in treating RA, characterized in that:

a) an RA patient is selected for treatment on the basis of the RA patient having at least one allele in the HLA-DRB1*04 allelic group; and

b) a therapeutically effective amount of an IL-17 antagonist is administered to the RA patient.

52. An IL-17 binding molecule for use in treating a patient having RA, characterized in that the IL-17 antagonist is to be administered to a patient that has at least one allele in the HLA-DRB1*04 allelic group.

53. An IL-17 binding molecule for use in treating a patient having RA, characterized in that the IL-17 antagonist is to be administered to a patient selected for treatment on the basis of having at least one allele in the HLA-DRB1*04 allelic group.

54. An IL-17 binding molecule for use in treating RA, characterized in that:

a) an RA patient is selected for treatment on the basis of the RA patient having a SE; and

b) a therapeutically effective amount of an IL-17 antagonist is administered to the RA patient.

55. An IL-17 binding molecule for use in treating a patient having RA, characterized in that the IL-17 antagonist is to be administered to a patient that has a SE.

56. An IL-17 binding molecule for use in treating a patient having RA, characterized in that the IL-17 antagonist is to be administered to a patient selected for treatment on the basis of having a SE.

57. The use according to any one of claims 51-56, characterized in that the IL-17 antagonist is to be administered intravenously to a patient in need thereof as three doses of about 10 mg/kg, each of the three doses being delivered every other week.

58. The use according to any one of claims 51-56, characterized in that the IL-17 antagonist is to be administered subcutaneously to the patient as a dose of about 75 mg - about 300 mg twice a month, monthly, every two months or every three months.

59. Use of an IL-17 antagonist in the manufacture of a medicament for use in treating a patient having RA, wherein the patient has at least one allele in the HLA-DRB1*04 allelic group.
60. Use of an IL-17 antagonist in the manufacture of a medicament for use in treating a patient having RA, wherein the patient is selected for treatment on the basis of having at least one allele in the HLA-DRB1*04 allelic group.
61. Use of an IL-17 antagonist in the manufacture of a medicament for use in treating a patient having RA, wherein the RA patient has a SE.
62. Use of an IL-17 antagonist in the manufacture of a medicament for use in treating a patient having RA, wherein the RA patient is selected for treatment on the basis of having a SE.
63. A method for determining the responsiveness of a patient having RA to treatment with an IL-17 antagonist, comprising
- a) performing an assay on a biological sample from the patient to determine the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and
 - b) assigning the patient as responsive to treatment with the IL-17 antagonist if the presence of the at least one allele is detected in the sample.
64. A method for determining the responsiveness of a patient having RA to treatment with an IL-17 antagonist, comprising
- a) performing an assay on a biological sample from the patient to determine the presence or absence of a SE; and
 - b) assigning the patient as responsive to treatment with the IL-17 antagonist if the presence of the at least one allele is detected in the sample.
65. A method for producing a transmittable form of information for use in predicting the responsiveness of a patient having RA to treatment with an IL-17 antagonist, comprising:
- a) assaying a biological sample from the patient for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group; and
 - b) embodying the result of the assaying step in a transmittable form of information.

66. A method for producing a transmittable form of information for use in predicting the responsiveness of a patient having RA to treatment with an IL-17 antagonist, comprising:

- a) assaying a biological sample from the patient for the presence or absence of a SE;
- and
- b) embodying the result of the assaying step in a transmittable form of information.

67. A method of predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist, comprising assaying a biological sample from the patient for the presence or absence of at least one allele in the HLA-DRB1*04 allelic group using an automatic analyzer, wherein the presence of the at least one allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the at least one allele is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.

68. A method of predicting the likelihood that a patient having RA will respond to treatment with an IL-17 antagonist, comprising assaying a biological sample from the patient for the presence or absence of a SE using an automatic analyzer, wherein the presence of the SE is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist and the absence of the SE is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist.

69. The method according to either claim 66 or 68, wherein the presence or absence of the SE is detected by assaying the biological sample for the presence or absence of at least one allele in the HLA-DRB1*SE allelic group.

70. The method, use or kit according to any of the above claims, wherein the presence or absence of the SE, the at least one allele in the HLA-DRB1*04 allelic group, or the at least one allele in the HLA-DRB1*SE allelic group is detected by a technique selected from the group consisting of Northern blot analysis, reverse transcription-polymerase chain reaction (RT-PCR), RT-PCR ELISA, TaqMan-based quantitative RT-PCR (probe-based quantitative RT-PCR), SYBR green-based quantitative RT-PCR, polymerase chain reaction (PCR), direct sequencing,

Sequence Specific Oligonucleotide (SSO) hybridization, Sequence Specific Primer (SSP) typing, and Sequence Based Typing (SBT), Southernblot, quantitative PCR (probe- or SYBR green-based), an immunoassay, immunohistochemistry, ELISA, flow cytometry, Western blot, HPLC, and mass spectrometry.

71. The method, use or kit according to any of the above claims, wherein said biological sample is selected from the group consisting of synovial fluid, blood, serum, plasma, urine, tear, saliva, cerebrospinal fluid, leukocyte sample and a tissue sample.
72. The method, use or kit according to any of the above claims, wherein the patient is a high risk RA patient.
73. A kit comprising:
- a) a pharmaceutical composition comprising an IL-17 antagonist for use in the treatment of rheumatoid arthritis (RA) in a patient; and
 - b) instructions describing how to administer said pharmaceutical composition to the patient, wherein the patient is characterized as having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group.
74. Use of an IL-17 antagonist in preparation of a medicament for the treatment of RA, provided that the patient is selected for the treatment on the basis of having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group.
75. Use of an IL-17 antagonist for the manufacture of a medicament for the treatment of RA in a patient characterized as having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group, wherein the medicament is formulated to comprise containers, each container having a sufficient amount of the IL-17 antagonist to allow delivery of at least about 75 mg – about 150 mg of the IL-17 antagonist per unit dose.
76. Use of an IL-17 antagonist for the manufacture of a medicament for the treatment of RA in a patient characterized as having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group, wherein the medicament is formulated to comprise containers,

each container having a sufficient amount of the IL-17 antagonist to allow delivery of at least about 10 mg of the IL-17 antagonist/kg patient weight per unit dose.

77. Use of an IL-17 antagonist for the manufacture of a medicament for the treatment of RA in a patient characterized as having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group, wherein the medicament is formulated at a dosage to allow intravenous delivery of about 10 mg of the IL-17 antagonist/kg patient weight per unit dose.

78. Use of an IL-17 antagonist for the manufacture of a medicament for the treatment of RA in a patient characterized as having a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group, wherein the medicament is formulated at a dosage to allow subcutaneous delivery of about 75 mg – about 150 mg of the IL-17 antagonist per unit dose.

79. An *in vitro* test method for selecting a patient for treatment of RA, comprising determining if the patient has a SE, an allele in the HLA-DRB1*04 allelic group, or an allele in the HLA-DRB1*SE allelic group.

80. The *in vitro* test method of claim 79, wherein the patient has an improved therapeutic response to the following regimen:

a) administering the patient three doses of about 10 mg/kg of an IL-17 antagonist, the first dose being delivered during week zero, the second dose being delivered during week two, and the third dose being delivered during week four; and

a) thereafter administering the patient about 75 mg - about 300 mg of the IL-17 antagonist twice a month, monthly, every two months or every three months, beginning during week eight.

81. The method, use or kit according to any of the above claims, wherein the IL-17 antagonist is an IL-17 binding molecule or an IL-17 receptor binding molecule.

82. The method, use or kit according to any of the above claims, wherein the patient has not been previously treated for RA with a TNF alpha antagonist.

83. The method, use or kit according to claim 81, wherein the IL-17 binding molecule or an IL-17 receptor binding molecule is an IL-17 binding molecule selected from the group consisting of:

- a) secukinumab;
- b) an IL-17 antibody that binds to an epitope of IL-17 comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129;
- c) an IL-17 antibody that binds to an epitope of IL-17 comprising Tyr43, Tyr44, Arg46, Ala79, Asp80;
- d) an IL-17 antibody that binds to an epitope of an IL-17 homodimer having two mature IL-17 protein chains, said epitope comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129 on one chain and Tyr43, Tyr44, Arg46, Ala79, Asp80 on the other chain;
- e) an IL-17 antibody that binds to an epitope of an IL-17 homodimer having two mature IL-17 protein chains, said epitope comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129 on one chain and Tyr43, Tyr44, Arg46, Ala79, Asp80 on the other chain, wherein the IL-17 binding molecule has a K_D of about 100-200 pM, and wherein the IL-17 binding molecule has an *in vivo* half-life of about 4 weeks; and
- f) an IL-17 antibody that comprises an antibody selected from the group consisting of:
 - 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; and

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.

84. The method, use or kit according to claim 82, wherein the IL-17 binding molecule is secukinumab.

Figure 1

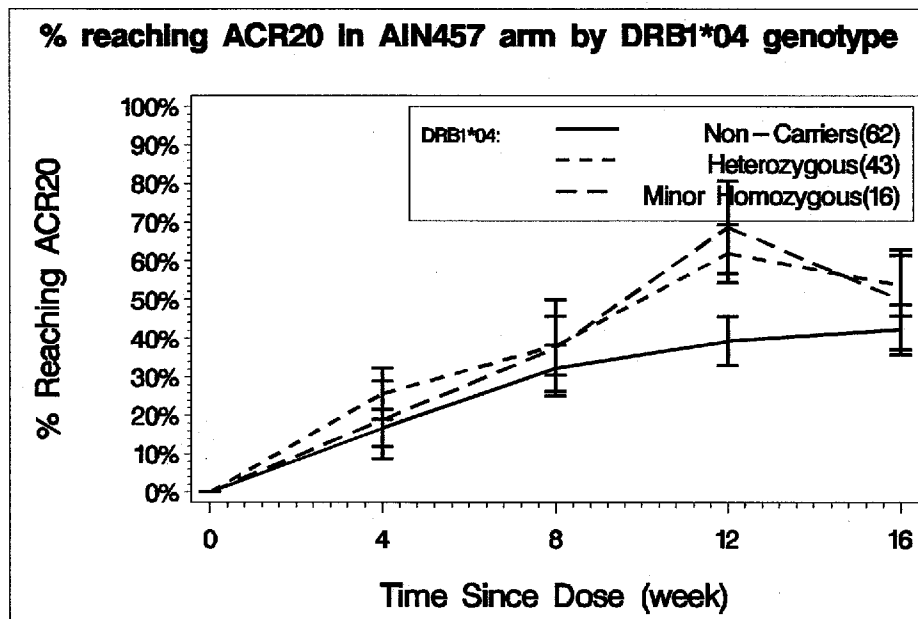


Figure 2

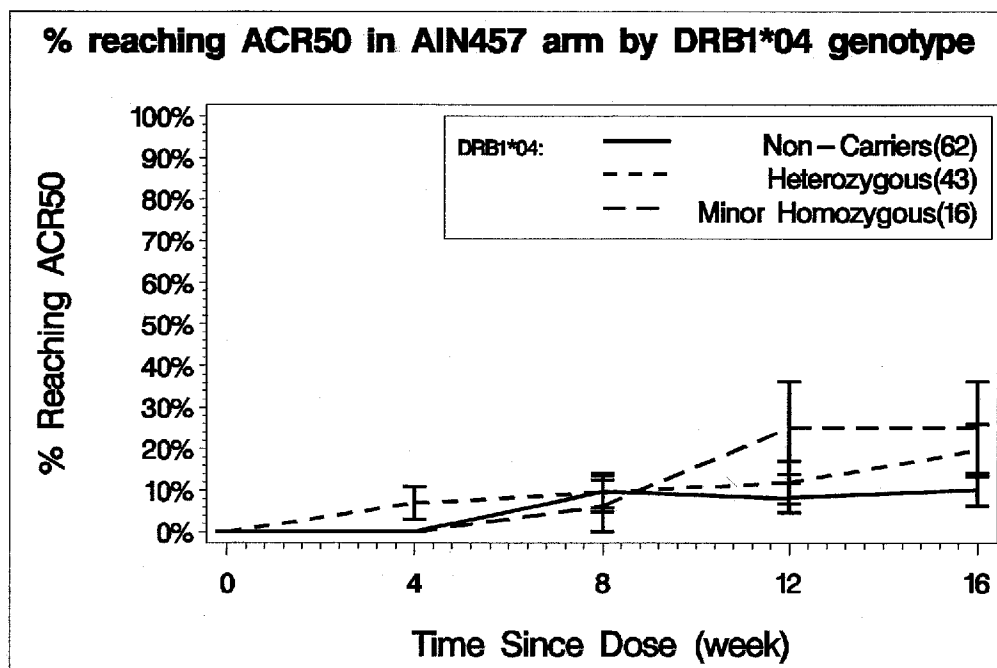


Figure 3

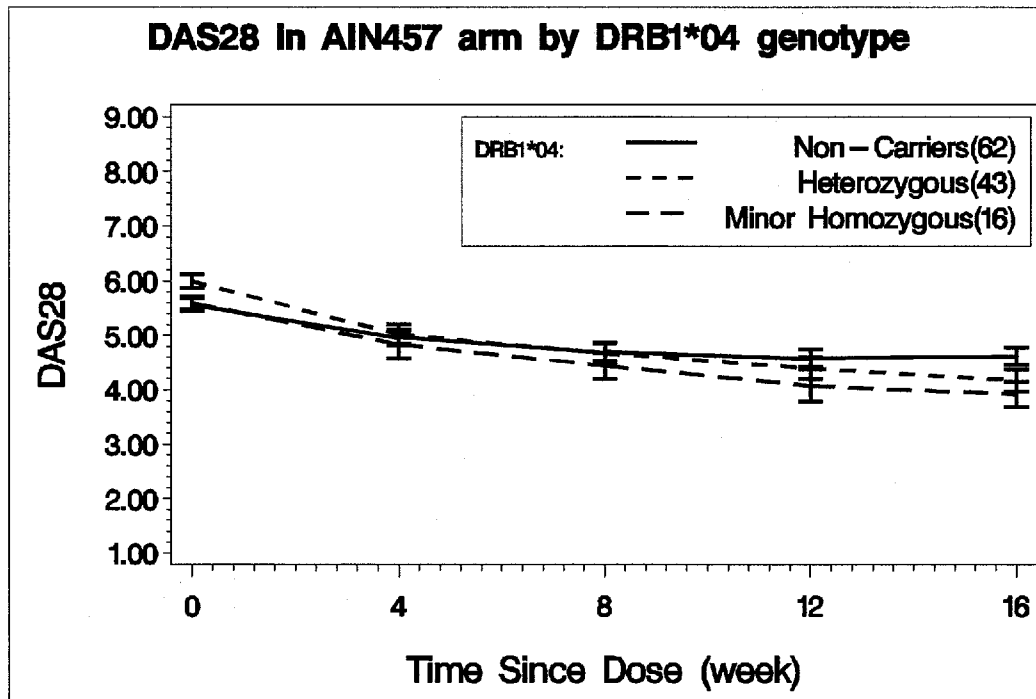


Figure 4

% reaching ACR50 by DRB1*04 genotype
All patients randomized to AIN457 at baseline

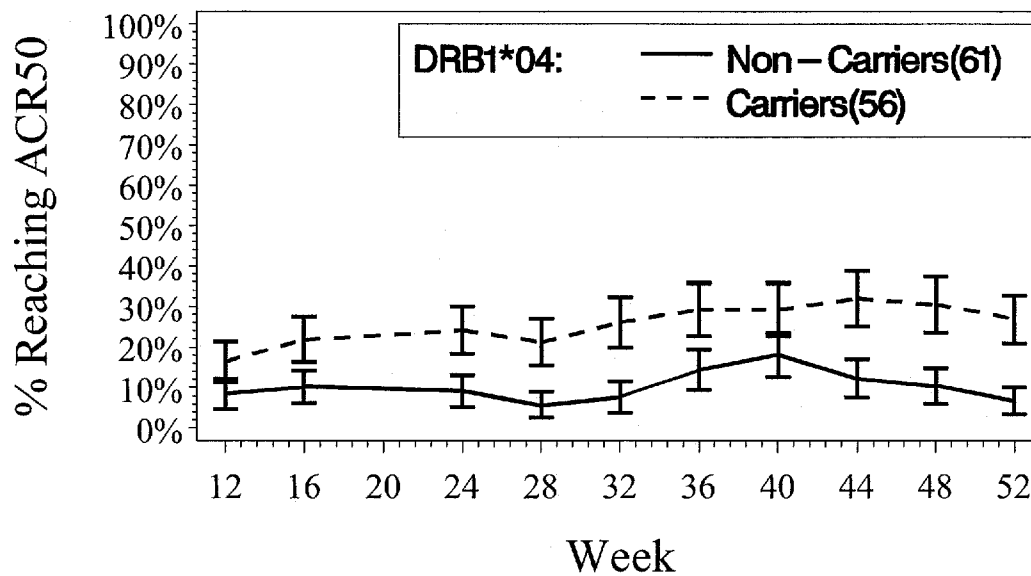


Figure 5

% reaching ACR20 by DRB1*04 genotype

All patients randomized to AIN457 at baseline

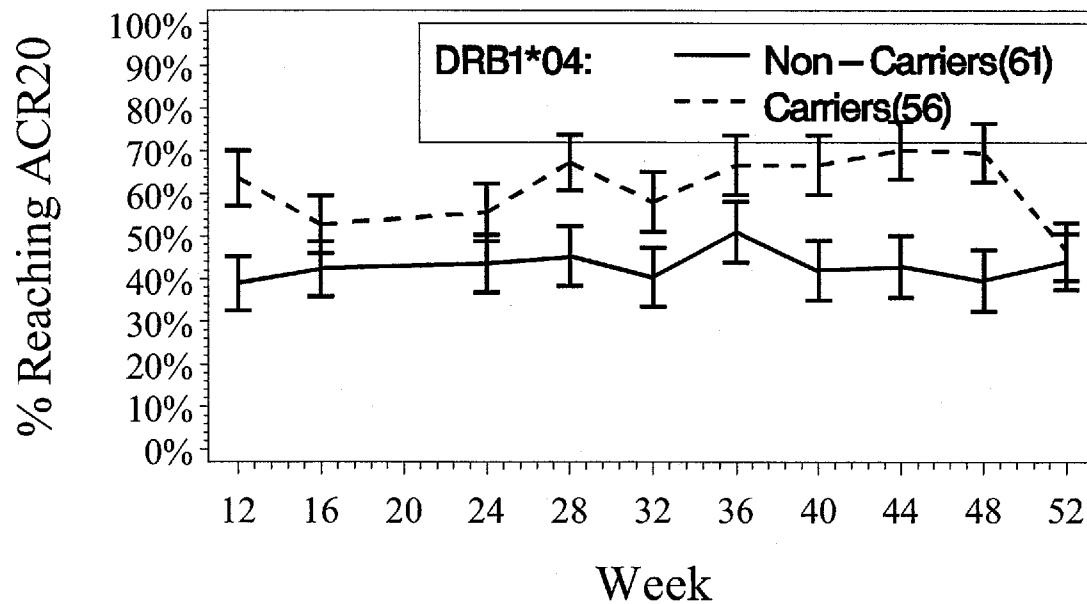


Figure 6

Mean Reduction from baseline DAS28 by DRB1*04 genotype

All patients randomized to AIN457 at baseline

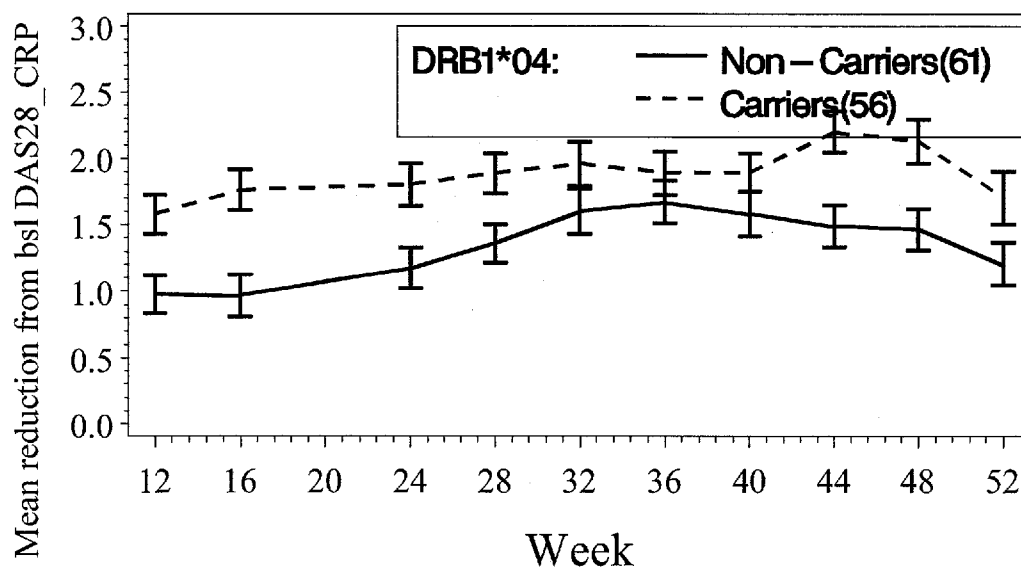


Figure 7

% reaching ACR50 by DRB1*04 genotype
AIN-treated patients defined as responders (ACR20) at week 16

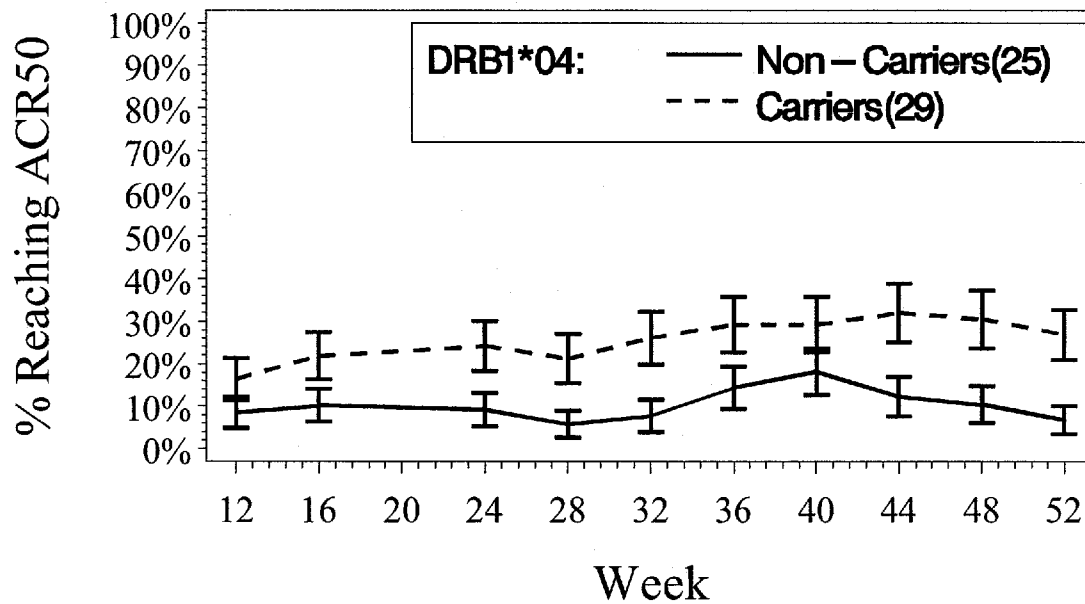


Figure 8

% reaching ACR20 by DRB1*04 genotype
AIN-treated patients defined as responders (ACR20) at week 16

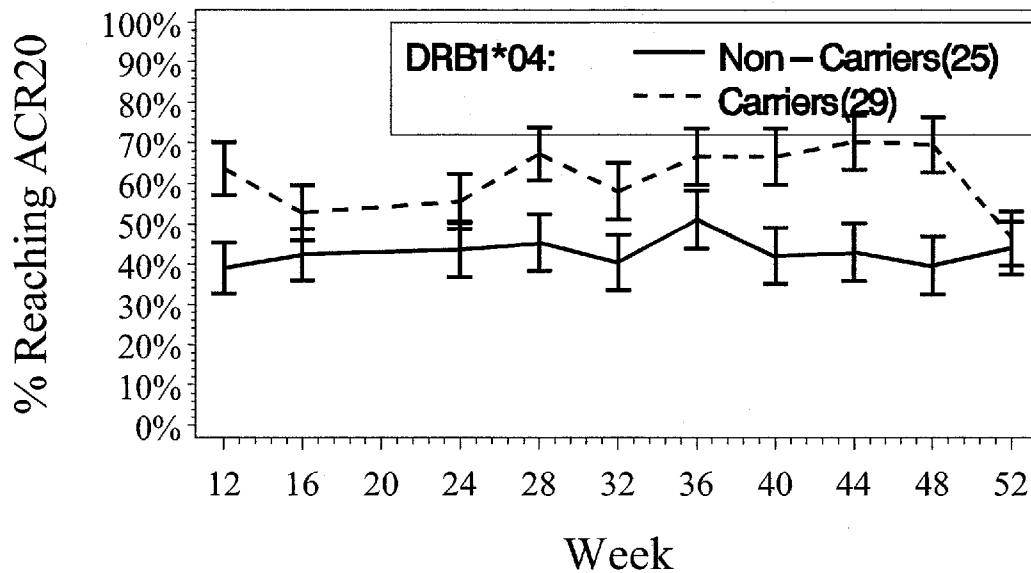
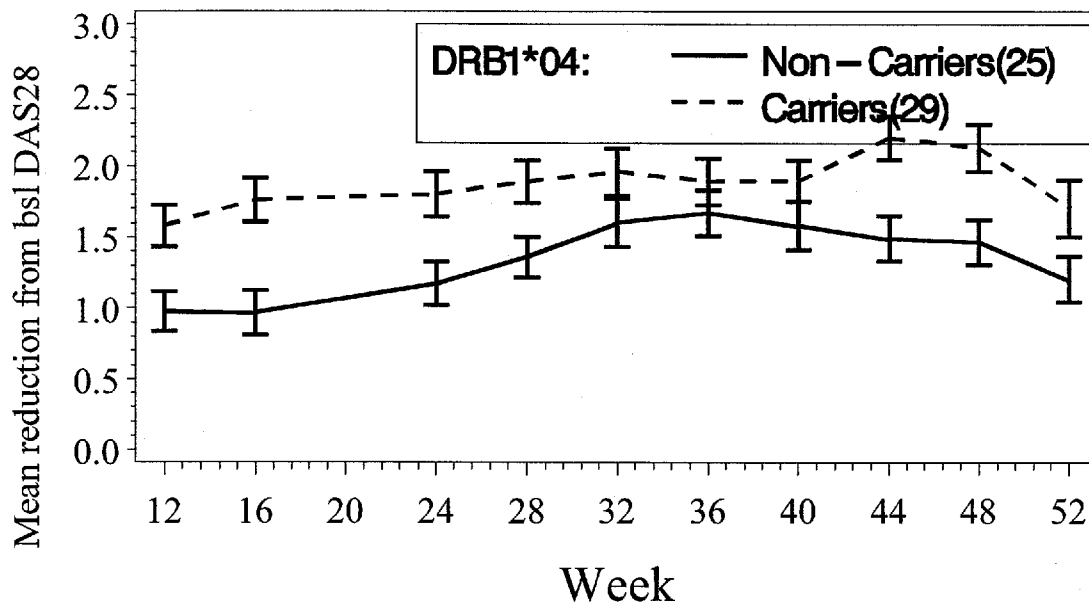


Figure 9

Mean Reduction from baseline DAS28 by DRB1*04 genotype
AIN-treated patients defined as responders (ACR20) at week 16

**Figure 10**

% reaching ACR50 by DRB1*04 genotype
Full placebo arm

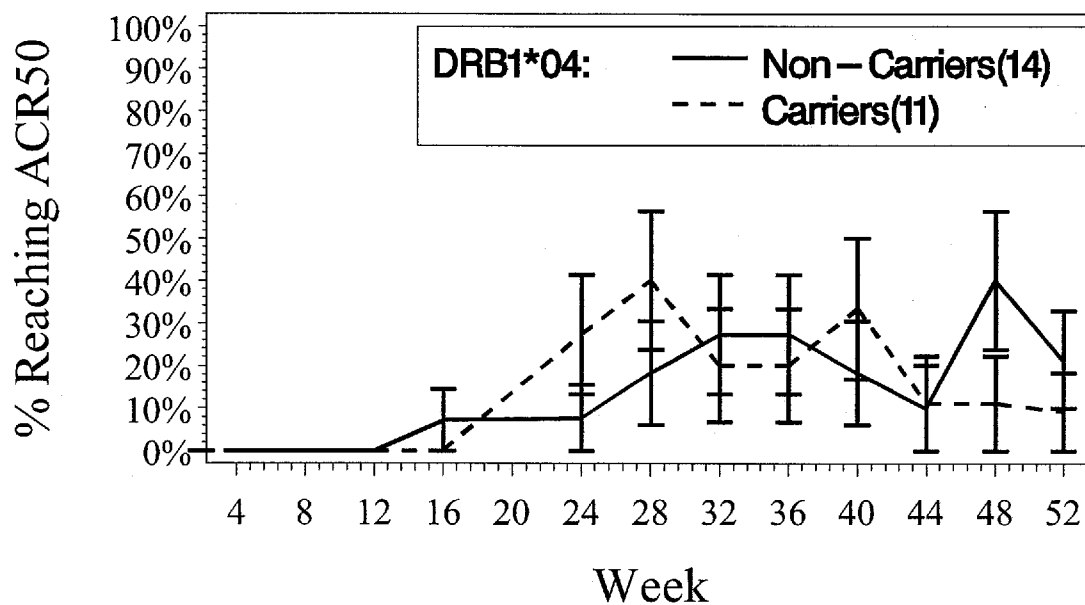


Figure 11

% reaching ACR20 by DRB1*04 genotype
Full placebo arm

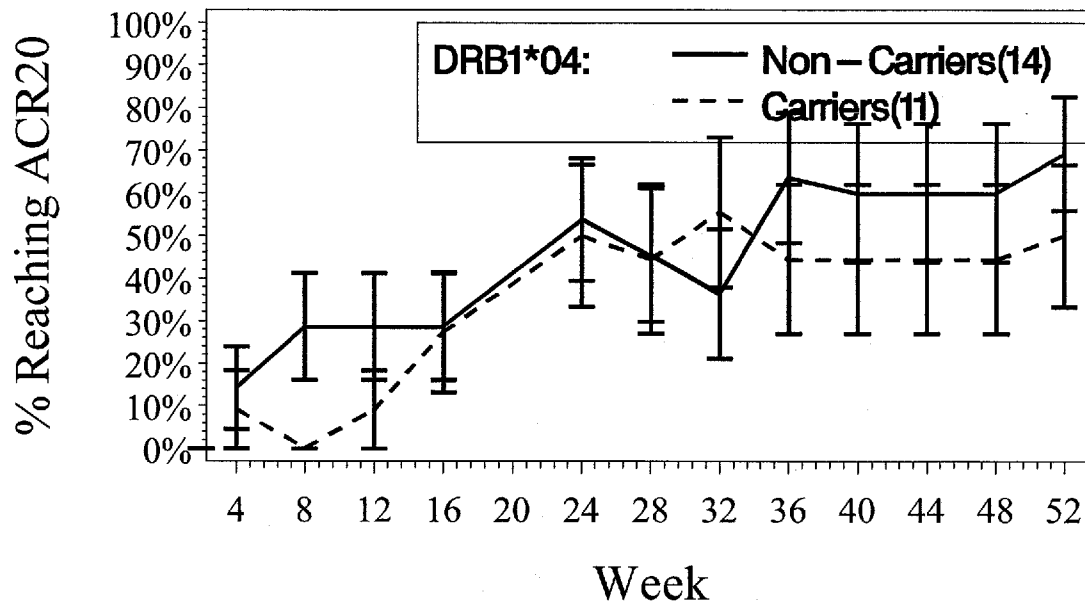


Figure 12

Mean Reduction from week-16 DAS28 by DRB1*04 genotype
Full placebo arm

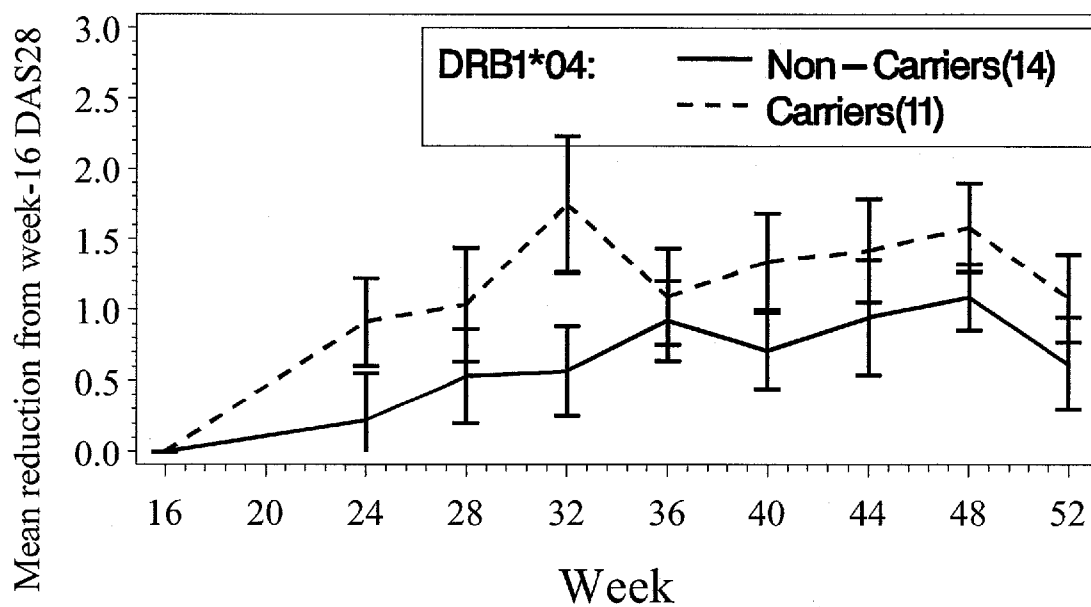


Figure 13

% reaching ACR50 by DRB1*04 genotype
Placebo arm patients not treated with anti-TNF before

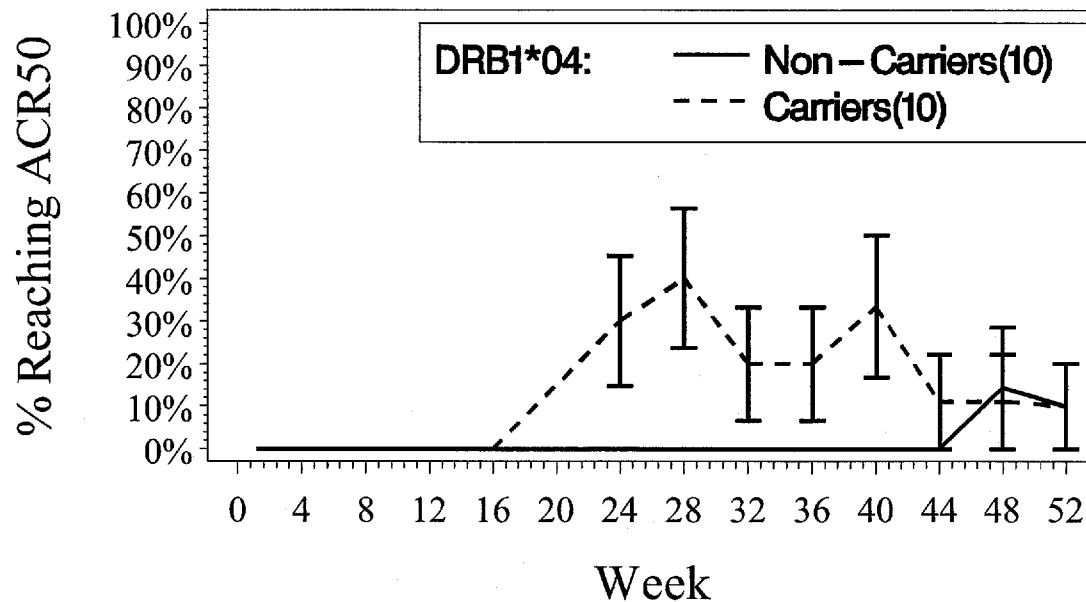


Figure 14

% reaching ACR20 by DRB1*04 genotype
Placebo arm patients not treated with anti-TNF before

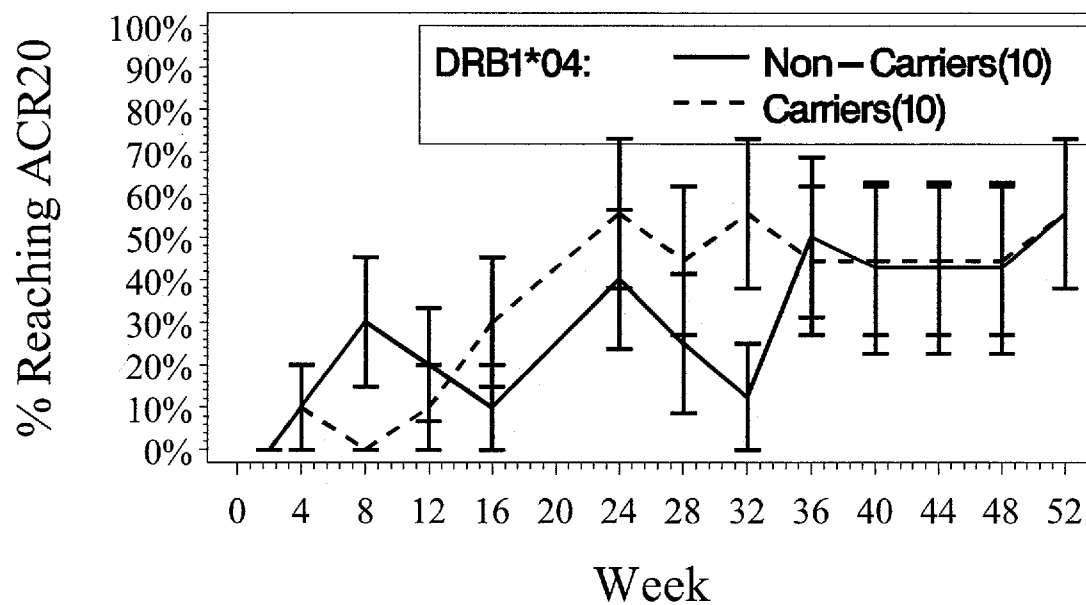
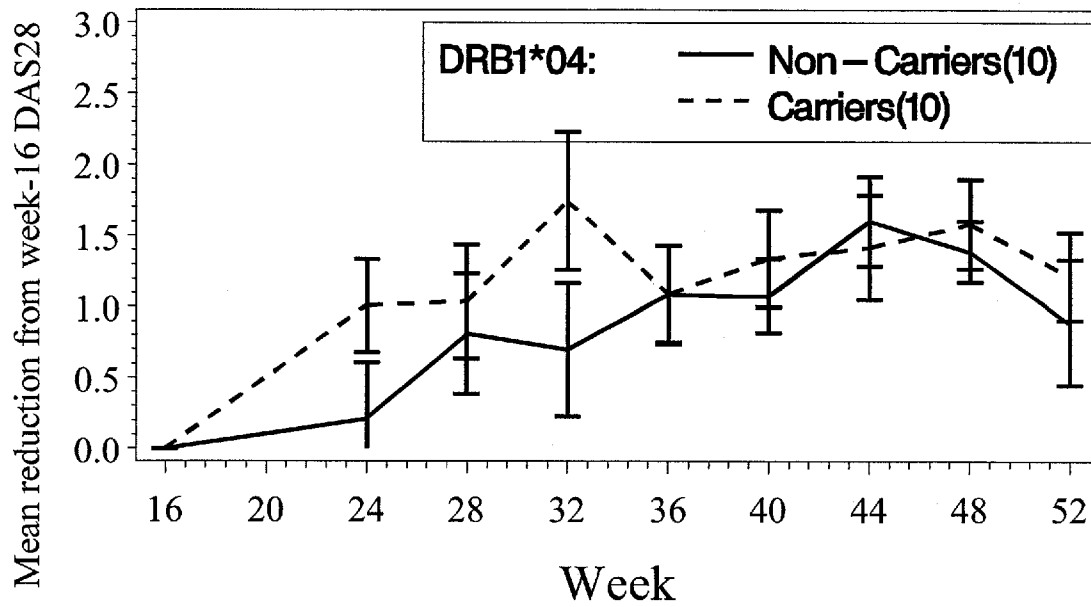


Figure 15

Mean Reduction from week-16 DAS28 by DRB1*04 genotype
Placebo arm patients not treated with anti-TNF before



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/064307

A. CLASSIFICATION OF SUBJECT MATTER INV. G01N33/68 A61P19/02 C12Q1/68 G01N33/564 A61K38/00 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) G01N C12Q		
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 practical, search terms used) EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	D. E. DE ALMEIDA ET AL: "Immune Dysregulation by the Rheumatoid Arthritis Shared Epitope", THE JOURNAL OF IMMUNOLOGY, vol. 185, no. 3, 30 June 2010 (2010-06-30) , pages 1927-1934, XP55019689, ISSN: 0022-1767, DOI: 10.4049/jimmunol.0904002 abstract; figure 8; discussion, in particular p.1933 col.1 last par. to col.2 -----	1-14, 21-58, 63-72, 80-84
A	WO 2010/034443 A1 (HOFFMANN LA ROCHE [CH]; ROCHE GLYCART AG [CH]; AUER JOHANNES [DE]; DIM) 1 April 2010 (2010-04-01) ----- -/--	1-14,16, 18-58, 63-72, 80-84
☒ 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 document 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 22 February 2012		Date of mailing of the international search report 02/03/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Behrens, Ralf

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/064307

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	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	16,18-20
Y	abstract; discussion, in particular penultimate paragraph -----	1-14, 21-58, 63-72, 80-84

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/064307

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/064307

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010034443 A1	01-04-2010	AR 073692 A1	24-11-2010
		AU 2009296299 A1	01-04-2010
		CA 2737636 A1	01-04-2010
		CN 102164959 A	24-08-2011
		CO 6351795 A2	20-12-2011
		EC SP11010911 A	31-05-2011
		EP 2331575 A1	15-06-2011
		MA 32725 B1	02-10-2011
		PE 03452011 A1	13-06-2011
		TW 201023882 A	01-07-2010
		US 2010080812 A1	01-04-2010
		WO 2010034443 A1	01-04-2010

Continuation of Box II.2

Claims Nos.: 15, 17, 59-62, 73-79(completely); 4, 5, 11, 18, 22, 29-32, 39-44, 47, 48, 54-58, 64, 66, 68, 70-72(partially)

The present application contains 84 claims, of which only 26 claims are dependent. There is no clear distinction between the independent claims because of overlapping scope. There are so many claims, and they are drafted in such a way that the claims as a whole are not in compliance with the provisions of clarity and conciseness of Article 6 PCT, as it is particularly burdensome for a skilled person to establish the subject-matter for which protection is sought. In addition, some of the subject-matter is not supported. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search (PCT Guidelines 9.19 and 9.25). The search was based on the subject-matter that, as far as can be understood, could reasonably be expected to be claimed later in the procedure, and the corresponding claims, namely

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2) declaration be overcome.