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(54) **Title**: METHODS OF TREATING AUTOIMMUNE DISEASES USING IL-17 ANTAGONISTS

(57) **Abstract**: The disclosure is directed to novel predictive methods and personalized therapies for treating an autoimmune disease (AI) selected from psoriasis, uveitis, rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and multiple sclerosis (MS). Specifically, this disclosure relates to methods of treating a patient having an AI disease by selectively administering an IL-17 antagonist, e.g., an IL-17 antibody, such as secukinumab, to the patient on the basis of that patient being genetically predisposed to have a favorable response to treatment with the IL-17 antagonist. Also disclosed herein are transmittable forms of information, diagnostic methods, and kits useful in predicting the likelihood that a patient having uveitis, RA, PsA, AS, psoriasis or MS will respond to treatment with an IL-17 antagonist, e.g., an IL-17 antibody, such as secukinumab.

METHODS OF TREATING AUTOIMMUNE DISEASES USING IL-17 ANTAGONISTS

RELATED APPLICATIONS

This application claims priority to U. S. Provisional Patent Application No 61/805,257 filed March 26, 2013, the disclosure of which is incoroporated by reference herein in its entirety.

TECHNICAL FIELD

The disclosure is directed to predictive methods, personalized therapies, kits, transmittable forms of information and methods for treating patients having an autoimmune disease selected from uveitis, rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), psoriasis, and multiple sclerosis (MS).

BACKGROUND OF THE DISCLOSURE

Autoimmune (AI) diseases are pathological disorders caused by a self-reactive immune response. AI diseases include, *inter alia*, rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), psoriasis, uveitis and multiple sclerosis (MS). While AI diseases are driven by both the innate and the adaptive immune response, the specificity of each AI disease is defined by particular autoantibodies, which may arise as a result of inflammation rather than acting as the causative agent of the particular AI disease. The etiology of the majority of AI diseases is unknown, although autoantibodies appear to be an essential link between the disease phenotypes and the genetic and/or environmental factors that trigger them.

Treatments for AI diseases vary, with immune suppression being a linking concept. Disease-modifying antirheumatic drugs (DMARDs), a heterogenous collection of agents grouped by use and convention, are the first line of treatment for RA. However, only about 2/3 of RA 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. 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.

The first-line drug treatments of mild AS are non-steroidal anti-inflammatory drugs (NSAIDs). Treatment of NSAIDs-refractory AS is hampered by the lack of efficacy of virtually all standard DMARDs, including MTX. As an exception, peripheral arthritis associated with AS responds quite well to sulfasalazine. TNF-blocking agents have been successfully used to treat AS (Braun J et al (2002) Lancet 359:1187-93) and demonstrate prolonged efficacy up to three years of follow-up (Braun et al. (2005) Rheumatology 44:670-6). However, upon discontinuation of TNF blockers, AS relapses quickly, indicating that the inflammatory process may only be suppressed by TNF blockade (Baraliakos et al (2005) Arthritis Rheum 53:856-63).

For treating PsA, traditional DMARDs, including MTX, sulfasalazine, cyclopsorine, and leflunomide and are generally considered inadequate for a number of patients because these drugs only partially control established disease (Mease PJ (2008) Psoriatic Arthritis. In: Klippel et al, eds. Primer on Rheumatic Diseases. 13th ed. New York: Springer Science, p. 170-192). Several clinical trials have demonstrated the efficacy of T cell targeted therapy in PsA (cyclosporine A, CTLA4 Ig, alefacept), and TNF blocking therapy has been successfully introduced for PsA treatment (Mease PJ et al. (2000) Lancet 356:385-90).

Traditional systemic treatments of moderate to severe psoriasis include the traditional DMARDs, MTX and cyclosporin. Safety, largely related to cumulative kidney and liver toxicity, is a major concern during long-term psoriasis treatment using cyclosporine and MTX, and requires frequent monitoring. Biological agents (infliximab, adalimumab and etanercept) are also employed in treating psoriasis. Unfortunately, adverse events have occurred to varying extent during chronic biologic treatment of psoriasis, most notably the reactivation of latent tuberculosis infections and the induction (or exacerbation of) demyelinating conditions due to TNF-alpha antagonisim (Ferrandiz et al. (2010) Clinics in Dermatology 28:81-87).

Several classes of products are approved for patients with relapsing forms of MS. However, because MS is a clinically and pathogenic heterogeneous disease, therapeutic response varies depending on the disease stage (early vs. late phases), disease course (relapsing remitting vs. secondary progressive vs. primary progressive) and level of disease activity (breakthrough vs. benign). Biologics, such as IFN-β, constitute the current first-line therapies with only modest efficacy (≈ 30-35% reduction of Annualized Relapse Rate [ARR] vs placebo). These products carry well-known safety and tolerability issues (e.g., flu-like syndrome). Natalizumab has superior efficacy (68% reduction of ARR vs placebo), but major safety risks. Mitoxantrone is

used in aggressive forms of MS, but its use is progressively declining, mainly due to the cumulative cardiac toxicity and well-known malignancy risk. Fingolimod, a first line therapy in the US and second line therapy in the rest of the world, shows superior benefit on relapses over IFN-β (54 and 52% reduction of ARR vs placebo and IFN-β). In general, switches between MS therapies are driven by a lack of efficacy and/or tolerability issues.

The only FDA-approved treatments for uveitis are the topical corticosteroid loteprednol and the ocular implant called Retisert® that delivers a corticosteroid (fluocinolone) over 30 months. Unfortunately, many cases of uveitis are not controlled with corticosteroids, or the dose of corticosteroids required to persistently suppress inflammation is higher than the Cushing threshold (about 8-10 mg prednisone equivalent/day). In such cases, one or more steroid-sparing immunosuppressive drugs are used off-label. However, there is a paucity of clinical trials comparing steroid-sparing drugs in uveitis, and there is no consensus among uveitis specialists about which steroid-sparing drugs are best for noninfectious uveitis in general or for many of the specific forms of noninfectious uveitis. In fact, regimens that are ardently advocated by some specialists are avoided by others.

Secukinumab (AIN457) is a high-affinity fully human monoclonal anti-human antibody that inhibits Interleukin-17A activity. In a series of recent studies, secukinumab has emerged as a desirable treatment for patients with various AI diseases, e.g., uveitis, RA, PsA, AS, psoriasis, and MS. However, because AI diseases are heterogeneous, patients will not necessarily respond to the same drug in the same way. Thus, stratification of AI disease patients using markers predictive of response will help clinicians select and establish an effective treatment strategy with IL-17 antagonists (such as secukinumab). Moreover, patient stratification will avoid the safety issues and the high financial burden associated with long-term therapy. Thus, there is a need to develop methods of treating AI diseases with IL-17 antagonists (such as secukinumab) that first identity those patients most likely to benefit from IL-17 antagonism.

BRIEF SUMMARY OF THE DISCLOSURE

While several single nucleotide polymorphisms (SNPs) are linked to various AI disease states (see, e.g, Wellcome Trust et al (2007) Nat Genet. 39(11):1329-37, Alzabin (2012) Expert Rev. Clin. Immunol. 8(2):111–113; Strange et al (2010) Nat. Genet. 42(11) 985-990; Huffmeier et al. (2010) Nat. Genet 42(11) 996-9; Ellinghaus et al.(2010) Nat. Genet 42(11) 991-5, etc.),

thus far no SNP has been identified as being predictive of whether a patient having a particular AI disease will respond to a treatment with an IL-17 antagonist. Provided herein are novel predictive methods and personalized therapies for patients having an AI disease (uveitis, RA, PsA, AS, psoriasis, or MS) that maximize the benefit and minimize the risk of IL-17 antagonism in these populations by identifying those patients likely to respond favorably prior to treatment with an IL-17 antagonist. This finding is based, in part, on the determinations that:

1) RA patients carrying at least one RA response marker selected from an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, and an rs11465770 response allele display improved response to secukinumab relative to RA patients that do not carry at least one of these alleles (or, in the case of the rs27689 response allele, relative to patients to do not carry both rs27689 response alleles);

2) PsA patients carrying at least one PsA response marker selected from an rs28096 response allele and two rs3819024 response alleles display improved response to secukinumab relative to PsA patients that do not carry at least one of these alleles (or, in the case of the rs3819024 response allele, relative to patient to do not carry both rs3819024 response alleles);

3) AS patients carrying at least one AS response marker selected from an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, and an rs11465770 response allele display improved response to secukinumab relative to AS patients that do not carry at least one of these alleles (or, in the case of the rs3819024 response allele, relative to patient to do not carry both rs3819024 response alleles);

4) psoriasis patients carrying an rs2241046 response allele display improved response to secukinumab relative to psoriasis patients that do not carry at least one of this allele;

5) MS patients carrying at least one MS response marker selected from an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles display improved response to secukinumab relative to MS patients that do not carry at least one of these alleles (or, in the case of the rs17066096 response allele, rs2546890 response allele, and rs2863212 response allele, relative to patients to do not carry both alleles);

6) uveitis patients carrying at least one uveitis response marker selected from an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, and an rs800292 response allele display improved response to secukinumab relative to uveitis patients that do not carry at least one of these alleles;

7) various SNPs in *ERAP1* are predictive of uveitis, MS, PsA and RA patient's response to IL-17 antagonism.

We thus contemplate that testing subjects for the presence of at least one of the afore-mentioned response alleles will be useful in a variety of pharmaceutical products and methods that involve identifying AI patients who are more likely to respond to IL-17 antagonsim and in helping physicians decide whether to prescribe IL-17 antagonists (e.g., secukinumab) to those patients or whether to prescribe an alternative pharmaceutical agent. Given our previous finding that an *ERAP1* SNP that results in a dysfunctional ERAP1 protein associates with an improved response to secukinumab in AS patients (US Provisional Patent Application No: 61/636,062, filed April 20, 2012; International Patent Application No. PCT/US2013/037068, filed April 18, 2013.), we also contemplate that testing subjects for the level of *ERAP1* expression, level of ERAP1 protein or level of ERAP1 activity will be useful in a variety of pharmacogenetic products and methods that involve identifying uveitis, AS, PsA, RA, MS and psoriasis patients more likely to respond to IL-17 antagonsim and in helping physicians decide whether to prescribe IL-17 antagonists (e.g., secukinumab) to those patients.

Accordingly, it is one object of the disclosure to provide methods of treating a patient having an AI disease selected from uveitis, RA, PsA, AS, psoriasis, and MS, by administering the patient a therapeutically effective amount of an IL-17 antagonist, e.g., an IL-17 antibody, such as secukinumab, based on certain aspects of the patient's biochemical profile. It is another object of the disclosure to provide methods of identifying a patient having an AI disease selected from uveitis, RA, PsA, AS, psoriasis, and MS who is more likely to respond to treatment of with an IL-17 antagonist, e.g., an IL-17 antibody, such as secukinumab, based on certain aspects of the patient's biochemical profile. It is another object of the disclosure to provide methods of determining the likelihood that a patient having an AI disease selected from uveitis, RA, PsA, AS, psoriasis, and MS will respond to treatment with an IL-17 antagonist, e.g., an IL-17 antibody, such as secukinumab, based on certain aspects of the patient's biochemical profile.

Disclosed herein are various methods of selectively treating a patient having an AI disease selected from uveitis, RA, PsA, AS, psoriasis, and MS. In some embodiments, these methods comprise assaying a biological sample from the patient for at least one of the disclosed AI response markers; and thereafter selectively administering a therapeutically effective amount of an IL-17 antagonist, e.g., secukinumab, to the patient if the patient has the at least one AI response marker. In other embodiments, these methods comprise assaying a biological sample from the patient for the level of *ERAP1* expression (e.g., mRNA, cDNA, etc.), the level of ERAP1 protein, and/or the level of ERAP1 activity; and thereafter selectively administering a therapeutically effective amount of an IL-17 antagonist, e.g., secukinumab, to the patient if the patient has a decreased level of *ERAP1* expression, decreased level of ERAP1 protein, and/or decreased level of ERAP1 activity relative to a control.

Disclosed herein are also various methods of predicting the likelihood that a patient having an AI disease selected from uveitis, RA, PsA, AS, psoriasis, and MS will respond to treatment with an IL-17 antagonist, e.g., secukinumab. In some embodiments, these methods comprise detecting at least one of the disclosed AI response markers in a biological sample from the patient, wherein the presence of the at least AI response marker is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist. In other embodiments, these methods comprise detecting the level of *ERAP1* expression (e.g., mRNA, cDNA, etc.), the level of ERAP1 protein, and/or the level of ERAP1 activity in a biological sample from the patient; wherein a decreased level of *ERAP1* expression, decreased level of ERAP1 protein, and/or decreased level of ERAP1 relative to a control is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist.

In preferred embodiments, the IL-17 antagonist is an IL-17 binding molecule, preferably a human antibody or antigen-binding portion thereof, most preferably secukinumab. In some embodiments, the AI response marker is at least one uveitis response marker, at least one RA response marker, at least one PsA response marker, at least one AS response marker, a psoriasis response marker, and/or a MS response marker as shown in **Table 1**. In some embodiments, the patient has multiple response markers as shown in **Table 1**.

In some embodiments, the patient is an RA patient. In some embodiments, the patient is a PsA patient. In some embodiments, the patient is a uveitis patient. In some embodiments, the

patient is an AS patient. In some embodiments, the patient is a psoriasis patient. In some embodiments, the patient is an MS patient.

Additional methods, uses, and kits 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.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows association of rs10484879 (located within an intron of *IL17A*) with secukinumab efficacy in RA trial F2201.

Figure 2 shows association of rs4711998 (located near *IL17A*) with secukinumab efficacy in RA trial F2201.

Figure 3 shows association of rs28096 (located within an intron of *ERAP1*) with secukinumab efficacy in PsA trial A2206.

Figure 4 shows association of rs27689 (located within an intron of *ERAP1*) with secukinumab efficacy in RA trials F2201 (**Fig. 4A**) and A2101 (**Fig. 4B**).

Figure 5 shows association of rs3214019 (located within an intron of *ERAP1*) with secukinumab efficacy in both RA trials F2201 (**Fig. 5A**) and A2101 (**Fig. 5B**).

Figure 6 shows association of rs72773968 (missense SNP in *ERAP1*) with secukinumab efficacy in RA trial F2201 (**Fig. 6A**) and MS trial B2201 (**Fig. 6B**).

Figure 7 shows association of rs10484879 (located within an intron of *IL17A*) with secukinumab efficacy in RA trial F2201 (**Fig. 7A**) and AS trial A2209 **(Fig. 7B).**

Figure 8 shows association of rs1937154 (located near *IL17A*) with secukinumab efficacy in RA trial F2201 (**Fig. 8A**) & AS trial A2209 **(Fig. 8B).**

Figure 9 shows association of rs3819024 (located within the promoter of *IL17A*) with secukinumab efficacy in PsA trial A2206 (**Fig. 9A**) & AS trial A2209 (**Fig. 9B**).

Figure 10 shows association of rs2241046 (located within an intron of *IL17RA*) with secukinumab efficacy in RA trial F2201 (**Fig. 10A**) & psoriasis trial A2211 (**Fig. 10B** and **10C**).

Figure 11 shows association of rs11465770 (located within an intron of *IL23R*) with secukinumab efficacy in RA trial F2201 (**Fig. 11A**), AS trial A2209 (**Fig. 11B**) and uveitis trial A2208 (**Fig. 11C**).

Figure 12 shows association of rs17066096 (located intergenic *IL20RA-IL22RA2*) with secukinumab efficacy in MS trial B2201.

Figure 13 shows association of rs2546890 (located in an intron of *IL12B*) with secukinumab efficacy in MS trial B2201.

Figure 14 shows association of rs1800693 (located in a splicing site of *TNFRSF1A*) with secukinumab efficacy in MS trial B2201.

Figure 15 shows association of rs2863212 (located in an intron of *IL23R*) with secukinumab efficacy in MS trial B2201.

Figure 16 shows association of rs72773968 (missense of *ERAP1*) with secukinumab efficacy in Uveitis trial A2208.

Figure 17 shows association of rs2241046 (located in an intron of *IL17RA*) with secukinumab efficacy in Uveitis trial A2208.

Figure 18 shows association of rs17482078 (missense of *ERAP1*) with secukinumab efficacy in Uveitis trial A2208.

Figure 19 shows association of rs800292 (missense of *CFH*) with secukinumab efficacy in Uveitis trial A2208.

DETAILED DESCRIPTION OF THE DISCLOSURE

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

The term “about” in relation to a numerical value x means +/-10% unless the cotext dictates otherwise.

As used herein, the terms "subject" and “patient” include 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.

The term "assaying" is used to refer to the act of identifying, screening, probing, testing measuring or determining, which act may be performed by any conventional means. For example, a sample may be assayed for the presence of a particular genetic or protein marker by using an ELISA assay, a Northern blot, imaging, serotyping, cellular typing, gene sequencing, phenotyping, haplotyping, immunohistochemistry, western blot, mass spectrometry, etc. The term "detecting" (and the like) means the act of extracting particular information from a given source, which may be direct or indirect. In some embodiments of the predictive methods disclosed herein, the presence of a given thing (e.g., allele, level of protein, etc.) is detected in a biological sample indirectly, e.g., by querying a database. 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.

The term "obtaining" means to procure, e.g., to acquire possession of in any way, e.g., by physical intervention (e.g., biopsy, blood draw) or non-physical intervention (e.g, transmittal of information via a server), etc.

The phrase "assaying a biological sample ..." and the like, is used to mean that a sample may be tested (either directly or indirectly) for either the presence of a given AI response marker. 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 probabiltity, then either the presence or the absence of such substance may be used to guide a therapeutic decision. For example, one may determine if a patient has AI response marker by determining the actual existence of particular response allele in the patient or by determining the absence of the particular response allele in the patient. In both such cases, one has determined whether the patient has the presence of the AI response marker. The disclosed methods involve, *inter alia*, determining whether a particular individual has an AI response marker. This determination is undertaken by identifying whether the patient has one or more of the AI response markers (i.e., uveitis response marker, RA response marker, PsA response marker, MS response marker, AS response marker, or psoriasis response marker) in **Table 1**. Each of these determinations (i.e., presence or absence), on its own, provides the allelic status of the patient and thus each of these deteriminations equally provide an indication of whether a particular individual would or would not respond more favorably to IL-17 antagonism.

Gene	SNP	Location	Disease (trial)	p value (response measure)	Response Allele (copies for response)[1]	Mode of Inheritance to obtain p value	Response Marker Family(ies)
IL-17A	rs10484879	Intronic	RA (F2201)	0.00017 (ACR20 week 16)	C (One / two)	Additive	RA Response Marker
IL-17A	rs4711998	Near	RA (F2201)	0.00094 (DAS28 week 16)	G (One)	Dominant	RA Response Marker
ERAP1	rs28096	Intronic	PsA	0.00054 (ACR50 week 6)	T (One / two)	Dominant	PsA Response Marker
ERAP1	rs27689	Intronic	RA (F2201)	0.038 (ACR50 week 16)	T (Two)	Dominant	RA Response Marker
			RA (A2101)	0.050 (ACR50 week 7)			
ERAP1	rs3214019	Intronic	RA (F2201)	0.045 (ACR50 week 16)	G (One)	Dominant	RA Response Marker
			RA (A2101)	0.009 (ACR50 week 7)			
ERAP1	rs72773968	Missense	RA (F2201)	0.027 (ACR20 week 16)	A (One / two)	Additive	RA Response Marker
			MS	0.023 (response)			MS Response Marker
			Uveitis	0.016 (response)			Uveitis Response Marker
IL-17A	rs10484879	Intronic	RA (F2201)	0.00017 (ACR20 week 16) 0.006 (DAS28 week 16)	C (One / two)	Additive	RA Response Marker
			AS	0.020 (ASAS40 week 6)	C (two)	Dominant	AS Response Marker
IL-17A	rs1937154	Near	RA (F2201)	0.013 (ACR20 week 16)	T (One / Two)	Additive	RA Response Marker
			AS	0.087 (ASAS40 week 6)			AS Response Marker
IL-17A	rs3819024	5' UTR, Promoter	PsA	0.074 (ACR20 week 6)	A (Two)	Dominant	PsA Response Marker
			AS	0.036 (ASAS56 week 6) 0.058 (ASAS40 week 6)			AS Response Marker
IL-17RA	rs2241046	Intronic	RA (F2201)	0.032 (DAS28)	C (One / two)	Dominant	RA Response Marker
			Psoriasis	0.017 (PASI75) 0.054 (PASI)		Additive	Psoriasis Response Marker
			Uveitis	0.006 (Response)		Dominant	Uveitis Response Marker
IL23R	rs11465770	Intronic	RA (F2201)	0.039 (DAS28 week 16)	(T) One	Dominant	RA Response Marker
			RA (F2208)	0.0074 (ACR50 week 10)			
			RA (F2206)	0.0021 (ACR50 week 12)			
			AS	0.012 (ASAS40 week 6)			AS Response Marker

				0.10 (ASAS20 week 6)			
			Uveitis	0.021 (change in V haze)			Uveitis Response Marker
IL20RA-IL22RA2	rs17066096	Intergenic	MS	0.0009 (Response)	A (Two)	Dominant	MS Response Marker
IL12B	rs2546890	Intronic	MS	0.0049 (Response)	G (Two)	Recessive	MS Response Marker
TNFRSF1A	rs1800693	splicing site	MS	0.055 (Response)	G (One / two)	Dominant	MS Response Marker
IL23R	rs2863212	Intronic	MS	0.0023 (Response)	T(Two)	Dominant	MS Response Marker
ERAP1	rs17482078	Missense	Uveitis	0.037 (Response)	T (One)	Dominant	Uveitis Response Marker
CFH	rs800292	Missense	Uveitis	0.040 (Remission)	C (One / two)	Additive	Uveitis Response Marker

Table 1 shows the various response alleles of the disclosure. Column 1 provides the gene in which the SNP of column 2 resides, and column 3 provides the general location of that SNP in that gene. Column 4 provides the indication for which the SNP has response-predictive value. The p value for a SNP (using the indicated disease measure) is presented in Column 5. Column 6 gives the nucleotide that associates with an improved response for a given SNP and provides the allelic dosage, i.e., one [homozygous or heterozygous] or two [i.e., homozygous], required to show improved response to secukinumab. Column 7 gives the mode of inheritance used in the analysis to get the p values as shown in column 5. Finally, Column 8 gives the broad family to which the respective response allele is assigned in the instant disclosure.

[1]Number 'one/ two' with additive mode of inheritance refers to dosage effect, where carriers of one copy of an allele show changed response relative to non-carriers, and carriers of two copies of the allele show changed response relative to carriers of only one copy of the allele.

Column 8 of **Table 1** gives the broad family to which the respective response allele (or two response alleles is assigned in the instant disclosure. Thus, as an example, "one rs28096 response allele" is a type of "PsA response marker", since PsA patients having at least one copy of this allele (i.e., heterozygous or homozygous for this allele) are more likely to have an improved response to secukinumab relative to PsA patients that do not have any doses of this allele. Similarly, "two rs3819024 response alleles" is also a "PsA response marker," since PsA patients having two copies of this allele (i.e., homozygous for this allele) are more likely to have an improved response to secukinumab relative to PsA patients that do not have two copies of this allele. Most SNPs listed in **Table 1** have predictive value for IL-17 antagonism if there is at least one copy of a given response allele (i.e., the patient is either homozygous or heterozygous for a given response allele). Moreover, the data provided herein shows that, for most of such response alleles, there is an additive mode of effect, i.e., the presence of one copy of the response allele is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist, and the presence of two response alleles is indicative of an even futher increased likelihood that the patient will respond to treatment with the IL-17 antagonist.

To provide an indication of increased responsiveness for an RA patient, a biological sample need only be assayed for one RA response marker, but clearly may be assayed for more than one of the RA response markers given in **Table 1**. To provide an indication of increased responsiveness for a uveitis patient, a biological sample need only be assayed for one uveitis response marker, but clearly may be assayed for more than one of the uveitis response markers given in **Table 1**. To provide an indication of increased responsiveness for a PsA patient, a biological sample need only be assayed for one PsA response marker, but clearly may be assayed for both of the PsA response markers given in **Table 1**. To provide an indication of increased responsiveness for an AS patient, a biological sample need only be assayed for one AS response marker, but clearly may be assayed for more than one of the AS response markers given in **Table 1**. To provide an indication of increased responsiveness for an MS patient, a biological sample need only be assayed for one MS response marker, but clearly may be assayed for more than one of the MS response markers given in **Table 1**. Because the instant disclosure provides only one psoriasis response marker, the phrase "psoriasis response marker" is used interchangeably with "rs2241046 response allele."

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 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.

"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 ideally 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 that bind to IL-17 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 ideally 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 VL) 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 hypervariable regions or 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, preferably an antibody to IL-17, e.g., secukinumab.

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 CDR. Exemplary antigen binding sites include the CDRs of secukinumab as set forth in SEQ ID NOs:1-6 and 11-13 (**Table 2**), 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.

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). The term "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. 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*, by N-nucleotide addition at junctions *in vivo* during recombination of antibody genes, or by somatic mutation *in vivo*). In some embodiments of the disclosed methods, regimens, kits, processes, uses and compositions, the IL-17 antagonist is a human antibody, an isolated antibody, and/or a monoclonal antibody.

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, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding portion 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.

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 about 10% of the measured parameter, by at least 50%, 80% or 90%, and in certain embodiments of the disclosed methods, uses, processes, kits and compositions, the IL-17 antibody used may inhibit greater than 95%, 98% or 99% of IL-17 functional activity.

"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 convienently 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 portion thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof) as disclosed herein typically has an IC_{50} 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 portion thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 receptor antibody or antigen-binding portion thereof) and functional derivatives thereof have an IC_{50} for inhibition of IL-6 production as defined above of about 20 nM or less, more preferably of about 10 nM or less, more preferably of about 5 nM or less, more preferably of about 2 nM or less, more preferably of about 1 nM or less.

The term "derivative", unless otherwise indicated, is used to define amino acid sequence variants, and covalent modifications (e.g., pegylation, deamidation, hydroxylation, phosphorylation, methylation, etc.) of an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding portion thereof) according to the present disclosure, e.g., of a specified sequence (e.g., a variable domain). 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. 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 (e.g., functional derivatives of secukinumab) 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)**, and substantially retain the ability to bind human IL-17 or, e.g., inhibit IL-6 production of IL-17 induced human dermal fibroblasts.

The phrase “substantially identical” means that the relevant amino acid or nucleotide sequence (e.g., 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 (e.g., conservative substitutions, such as swapping a serine for a threonine, or substitutions at positions not involved in antibody activity, structural integrity, complement fixation, etc.) in a 5 amino acid sequence of a specified region (e.g., V_H or V_L domain). 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 disclosure. In some embodiments, the sequence identity of a derivative IL-17 antibody (e.g., a derivative of secukinumab, e.g., a secukinumab biosimilar antibody) can be about 90% or greater, e.g., 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher relative to the disclosed sequences.

"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 Altshul et al. ((1990) J. Mol. Biol., 215: 403 410); the algorithm of Needleman et al. ((1970) J. Mol. Biol., 48: 444 453); or the algorithm of Meyers et al. ((1988) Comput. Appl. Biosci., 4: 11 17). A set of parameters may be the Blosum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5. The percent identity between two amino acid or nucleotide sequences can also be determined using the algorithm of E. Meyers and W. Miller ((1989) CABIOS, 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

"Amino acid(s)" refer to all naturally occurring L-α-amino acids, e.g., and include D-amino acids. The phrase "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).

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

The term "administering" in relation to a compound, e.g., an IL-17 binding molecule or another agent, is used to refer to delivery of that compound to a patient by any route.

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 portion thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding portion thereof) that is effective, upon single or multiple dose administration to a patient (such as a human) for 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 the case may be) 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.

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 (e.g., secukinumab) shows a clinically meaningful benefit from said treatment. In the case of RA and PsA, such criteria include, e.g., ACR20, ACR50, ACR70, DAS28, etc. In the case of AS, such criteria include, e.g., ASAS40, ASAS56, etc. In the case of psoriasis, such criteria include, e.g., PASI, PASI75, etc. Other criteria include MRI scans, vitreous haze analysis, neural scans, etc. All such criteria are acceptable measures of whether a patient is responding to a given treatment. The phrase "respond to treatment" is meant to be construed comparatively, rather than as an absolute response. For example, an RA patient having an RA response marker is predicted to have more benefit from treatment with an IL-17 antagonist than an RA patient who does not have the RA response marker. These carriers of RA response markers 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 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.

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 on the basis of (due to) the particular patient having a predetermined criteria, e.g., the patient has an AI response marker (i.e., an RA response marker, a uveitis response marker, an AS response marker, a PsA response marker, a psoriasis response marker, or a MS response marker). Similarly, "selectively treating" refers to providing treatment to a patient having a particular disease, where that patient is specifically chosen from a larger group of patients on the basis of the particular patient having a predetermined criteria, e.g., an RA patient specifically chosen for treatment due to the patient having a RA response marker. Similarly, "selectively administering" refers to administering a drug to a patient that is specifically chosen from a larger group of patients on the basis of (due to) the particular patient having a predetermined criteria, e.g., a particular genetic or other biological marker. By selecting, selectively treating and selectively administering, it is meant that a patient is delivered a personalized therapy based on the patient's particular biology, rather than being delivered a standard treatment regimen based solely on the patient having a particular disease. Selecting, in reference to a method of treatment as used herein, does not refer to fortuitous

treatment of a patient that has an AI response marker, but rather refers to the deliberate choice to administer an IL-17 antagonist to a patient based on the patient having an AI response marker. Thus, selective treatment differs from standard treatment, which delivers a particular drug to all patients, regardless of their allelic status.

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 an AI disease selected from uveitis, RA, PsA, AS, psoriasis and MS 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 interchangably 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 phrase "increased likelihood" refers to an increase in the probability that an event will occur. For example, some 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 patient having an AI disease selected from uveitis, RA, PsA, AS, psoriasis and MS who does not have an AS response marker (i.e.,a uveitis response marker, an RA response marker, an AS response marker, a PsA response marker, a psoriasis response marker, or a MS response marker).

As used herein "SNP" refers to "single nucleotide polymorphism". A single nucleotide polymorphism is a DNA sequence variation occurring when a single nucleotide in the genome (or other shared sequence) differs between members of a biological species or paired chromosomes in an individual. Most SNPs have only two alleles, and one is usually more common in the population. A SNP may be present in an exon or an intron of a gene, an upstream or downstream untranslated region of a gene, or in a purely genomic location (i.e., non-

transcribed). When a SNP occurs in the coding region of a gene, the SNP may be silent (i.e., a synonymous polymorphism) due to the redundancy of the genetic code, or the SNP may result in a change in the sequence of the encoded polypeptide (i.e., a non-synonymous polymorphism). In the instant disclosure, SNPs are identified by their Single Nucleotide Polymorphism Database (dbSNP) rs number, e.g., "rs4263839". The dbSNP is a free public archive for genetic variation within and across different species developed and hosted by the National Center for Biotechnology Information (NCBI) in collaboration with the National Human Genome Research Institute (NHGRI).

A polymorphic site, such as a SNP, is usually preceded by and followed by conserved sequences in the genome of the population of interest and thus the location of a polymorphic site can often be made in reference to a consensus nucleic acid sequence (e.g., of thirty to sixty nucleotides) that bracket the polymorphic site, which in the case of a SNP is commonly referred to as the "SNP context sequence". Context sequences for the SNPs disclosed herein may be found in the NCBI SNP database available at: www.ncbi.nlm.nih.gov/snp. Alternatively, the location of the polymorphic site may be identified by its location in a reference sequence (e.g., GeneBank deposit) relative to the start of the gene, mRNA transcript, BAC clone or even relative to the initiation codon (ATG) for protein translation. The skilled artisan understands that the location of a particular polymorphic site may not occur at precisely the same position in a reference or context sequence in each individual in a population of interest due to the presence of one or more insertions or deletions in that individual's genome as compared to the consensus or reference sequence. It is routine for the skilled artisan to design robust, specific and accurate assays for detecting the alternative alleles at a polymorphic site in any given individual, when the skilled artisan is provided with the identity of the alternative alleles at the polymorphic site to be detected and one or both of a reference sequence or context sequence in which the polymorphic site occurs. Thus, the skilled artisan will understand that specifying the location of any polymorphic site described herein by reference to a particular position in a reference or context sequence (or with respect to an initiation codon in such a sequence) is merely for convenience and that any specifically enumerated nucleotide position literally includes whatever nucleotide position the same polymorphic site is actually located at in the same locus in any individual being tested for the genetic marker of the invention using any of the genotyping methods described herein or other genotyping methods known in the art.

In addition to SNPs, genetic polymorphisms include translocations, insertions, substitutions, deletions, etc., that occur in gene enhancers, exons, introns, promoters, 5' UTR, 3'UTR, etc.

As used herein "rs10484879" refers to an A/C (rev) SNP located within an intron of the human *IL-17A* gene (GeneBank Accession No. NM_002190.2). The IL-17A gene encodes the IL-17A cytokine, which is involved in the Th17 pathway, and various autoimmine and inflammatory responses. The rs10484879 polymorphic site is located at chromosomal postion 52051957 (build 37.3; assembly GRCh37.p5), which is position 51991957 of Contig NT_007592.15. The phrase "rs10484879 response allele" as used herein refers to the the "C" allele ("G" allele, in the case of the complementary strand) at the rs10484879 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has at least one rs10484879 response allele.

As used herein "rs4711998" refers to an A/G (fwd) SNP located near the human *IL-17A* gene (GeneBank Accession No. NM_002190.2). The rs4711998 polymorphic site is located at chromosomal postion 52050353 (build 37.3; assembly GRCh37.p5), which is position 51990353 of Contig NT_007592.15. The phrase "rs4711998 response allele" as used herein refers to the the "G" allele ("C" allele, in the case of the complementary strand) at the rs4711998 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has at least one rs4711998 response allele.

The *ERAP1* gene encodes the ERAP1 protein, a multifunctional enzyme involved in cytokine receptor cleavage and trimming of peptides for presentation by major histocompatibility complex (MHC) class I molecules. Several polymorphisms in ERAP1 have been associated with chronic inflammatory diseases, including AS, psoriasis, and MS. As used herein, "rs30187" refers to a T/C SNP in the human *ERAP1* gene located on chromosome 5, which is associated with both AS and MS (Wellcome Trust et al (2007) Nat Genet. 39(11):1329-37; M. Brown (2008) Rheumatology 47(2):132-7; Guerini et al. (2012) PLoS One 7(1)e29931). The rs30187 polymorphic site is located at chromosomal position 96,150,086 (NCBI genome build 36.3), position 30,519 of the human *ERAP1* gene set forth as GeneBank Accession No. NG_027839.1, position 1,688 of the human ERAP1 transcript variant 3 mRNA set forth as GeneBank Accession No. NM_001198541, position 1,930 of the human ERAP1 transcipt variant 2 mRNA set forth as GeneBank Accession No. NM_001040458; codon encoding amino acid 528 of the human

ERAP1 protein set forth as GeneBank Accession No. NP_057526.3). The rs30187 "C" allele encodes a K528R variant of *ERAP1* that has impaired catalytic properties, and is associated with reduced incidence of AS. (Kochan et al. (2011) Proc Natl Acad Sci U S A. 108(19):7745-50). Each "T" allele of rs30187 increases the odds of having AS by about 1.4x. We have previously determined that AS patients having a rs30187 "T" allele display decreased secukinumab response (US Provisional Patent Application 61/636,062, which is incorporated by reference herein in its entirety).

As used herein, the term "rs27434" refers to an A/G SNP in the human *ERAP1* gene. (Lin et al. (2011) J Rheumatol. 38(2):317-21). The rs27434 polymorphic site is located at position 25,337 of the human *ERAP1* gene set forth as GeneBank Accession No. NG_027839.1 (position 1,415 of the human *ERAP1* mRNA set forth as GeneBank Accession No. NM_016442.3; codon encoding amino acid 356 of the human ERAP1 protein set forth as GeneBank Accession No. NP_057526.3). The rs27434 SNP is a synonymous polymorphism occuring in the codon for Ala356 of the ERAP1 protein. (Harvey et al. (2009) Hum. Mol. Genet. 18 (21): 4204-4212). Each "A" disease allele of rs27434 increases the odds of having AS by about 1.19x. We have previously determined that AS patients having a rs27434 "A" allele display decreased response to secukinumab (US Provisional Patent Application 61/636,062, which is incorporated by reference herein in its entirety).

As used herein "rs27689" refers to a G/T SNP located in an intron of the human *ERAP1* gene (position 47647 of GeneBank Accession No. NG_027839.1). The *ERAP1* mRNA sequence is found in GeneBank Accession No. NM_016442.3. The rs27689 polymorphic site is located at chromosomal postion 96107202 (build 37.3; assembly GRCh37.p5), which is position 4421074 of Contig NT_034772.6. The phrase "rs27689 response allele" as used herein refers to the the "T" allele ("A" allele, in the case of the complementary strand) at the rs27689 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has two rs27689 response alleles.

As used herein "rs3214019" refers to an A/G SNP located in an intron of the human *ERAP1* gene (position 110370 of GeneBank Accession No. NG_029490.1). The *ERAP1* mRNA sequence is found in GeneBank Accession No. NM_001042440.2. The rs3214019 polymorphic site is located at chromosomal postion 96103110 (build 37.3; assembly GRCh37.p5), which is position 4416982 of Contig NT_034772.6. The phrase "rs3214019 response allele" as used

herein refers to the the "G" allele ("C" allele, in the case of the complementary strand) at the rs3214019 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has at least one rs3214019 response allele.

As used herein "rs72773968" refers to an A/G SNP located in an exon of the human *ERAP1* gene (position 15254 of GeneBank Accession No. NG_027839.1). The rs72773968 polymorphic site is located at chromosomal postion 96139595 (build 37.3; assembly GRCh37.p5), which is position 4453467 of Contig NT_034772.6. The rs72773968 polymorphic site is located at position 382 of *ERAP1* mRNA GeneBank Accession No. NM_001040458.1 and position 140 of GeneBank Accession No. NM_001198541.1. When a "T" replaces a "C" at this position, the resulting missense mutation is a Thr → Ile at position 12 of the ERAP1 protein (position 12 of NP_001035548.1 and NP_001185470.1). The phrase "rs72773968 response allele" as used herein refers to the the "A" allele (T allele, in the case of the complementary strand) at the rs72773968 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has at least one rs72773968 response allele.

As used herein "rs17482078" refers to a C/T SNP located in an exon of the human *ERAP1* gene (position 35983 of GeneBank Accession No. NG_027839.1). The rs17482078 polymorphic site is located at chromosomal postion 96118866 (build 37.3; assembly GRCh37.p5), which is position 4432738 of Contig NT_034772.6. The rs17482078 polymorphic site is located at position 2521 of *ERAP1* mRNA GeneBank Accession No. NM_001040458.1 and position 2279 of GeneBank Accession No. NM_001198541.1. When an "A" replaces a "G" at this position, the resulting missense mutation is a Arg → Gln at position 725 of the ERAP1 protein (position 725 of NP_001035548.1 and NP_001185470.1). The phrase "rs17482078 response allele" as used herein refers to the the "T" allele ("A" allele, in the case of the complementary strand) at the rs17482078 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has at least one rs17482078 response allele. Bettencourt et al. (2013) Rheumatology (Oxford) 52(12):2168-76 showed that rs17482078 "A" allele (Arg725Gln) provided a protective effect from AS in HLA-B27 positive individuals. According to Evans et al. (2011) Nat. Genet. 43(8):761-67, both the protective rs30187 and rs17482078 alleles have ~40% slower rates of substrate trimming than wild-type ERAP1 ($P = 0.050$, Wilcoxon rank sum test, one-tailed exact test), suggesting that both represent loss-of-function variants.

As used herein "rs1937154" refers to a C/T SNP located near the human *IL-17A* gene. The rs1937154 polymorphic site is located at chromosomal postion 52057735 (build 37.3; assembly GRCh37.p5), which is position 51997735 of Contig NT_007592.15. The phrase "rs1937154 response allele" as used herein refers to the the "T" allele (A allele, in the case of the complementary strand) at the rs1937154 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has at least one rs1937154 response allele.

As used herein "rs2241046" refers to a C/T SNP located in an intron of the human *IL-17RA* gene (position 25621 of GeneBank Accession No. NG_028257.1). The *IL17RA* gene encodes the IL-17 cytokine receptor, which is involved in the Th17 pathway, and various autoimmine and inflammatory responses. The sequence of *IL-17RA* mRNA is found in GeneBank Accession No. NM_014339.5. The rs2241046 polymorphic site is located at chromosomal postion 17586471 (build 37.3; assembly GRCh37.p5), which is position 738621 of Contig NT_011519.10. The phrase "rs2241046 response allele" as used herein refers to the the "C" allele (G allele, in the case of the complementary strand) at the rs2241046 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has at least one rs2241046 response allele.

As used herein "rs11465770" refers to a C/T SNP located in an intron of the human *IL-23R* gene (position 6795 of GeneBank Accession No. NG_011498.1). The *IL23R* gene encodes the IL-23 cytokine receptor, which is involved in the Th17 pathway, and various autoimmine and inflammatory responses. The sequence of *IL-23R* mRNA is found in GeneBank Accession No. NM_144701.2. The rs11465770 polymorphic site is located at chromosomal postion 67633963 (build 37.3; assembly GRCh37.p5), which is position 37605881 of Contig NT_032977.9. The phrase "rs11465770 response allele" as used herein refers to the the "T" allele (A allele, in the case of the complementary strand) at the rs11465770 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has at least one rs11465770 response allele. As used herein "rs28096" refers to an A/G SNP located in an intron of the human *ERAP1* gene (position 45605 of GeneBank Accession No. NG_027839.1). The sequence of *ERAP1* mRNA is found in GeneBank Accession No. NM_016442.3. The rs28096 polymorphic site is located at chromosomal postion 96109244 (build 37.3; assembly GRCh37.p5), which is position 4423116 of Contig NT_034772.6. The phrase "rs28096 response allele" as used herein refers to the the "T" allele ("A" allele, in the case of the complementary strand) at the rs28096 polymorphic site.

In some embodiments of the disclosed methods, uses, and kits, the patient has at least one rs28096 response allele.

As used herein "rs3819024" refers to an A/G SNP located in the promoter for the human *IL-17A* gene. The sequence of *IL-17A* mRNA is found in GeneBank Accession No. NM_002190.2. The rs3819024 polymorphic site is located at chromosomal postion 52050786 (build 37.3; assembly GRCh37.p5), which is position 51990786 of Contig NT_007592.15. The phrase "rs3819024 response allele" as used herein refers to the the "A" allele (T allele, in the case of the complementary strand) at the rs3819024 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has two rs3819024 response alleles.

As used herein, "rs17066096" refers to an A/G SNP located intergenic between the human *IL20RA* and *IL22RA2* genes. The rs17066096 polymorphic site is located at chromosomal postion 137452908 (build 37.3; assembly GRCh37.p5), which is position 41622365 of Contig NT_025741.15. rs17066096-G is risk allele of MS (Patsopoulos NA, et al, 2011). The phrase "rs17066096 response allele" as used herein refers to the "A" allele ("T" allele, in the case of the complementary strand) at the rs17066096 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has two rs17066096 response alleles.

As used herein, "rs2546890" refers to an A/G SNP located in an intron of the human *IL-12B* gene. The rs2546890 polymorphic site is located at chromosomal postion 158759900 (build 37.3; assembly GRCh37.p5), which is position 3571173 of Contig NT_023133.13, which is also position 2582 of GeneBank Accession No. NG_009618.1 and position 634 of GeneBank Accession No. NR_037889.1. rs2546890-A is risk allele of MS (Patsopoulos NA et al, 2011). The *IL12B* gene encodes the IL-12B cytokine, which is a cytokine that acts on T and natural killer cells, and has a broad array of biological activities. The phrase "rs2546890 response allele" as used herein refers to the the "G" allele ("C" allele, in the case of the complementary strand) at the rs2546890 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has two rs2546890 response alleles.

As used herein, "rs1800693" refers to an A/G SNP located in splicing site of the human *TNFRSF1A* gene. The rs1800693 polymorphic site is located at chromosomal postion 6440009 (build 37.3; assembly GRCh37.p5), which is position 6380009 of Contig NT_009759.16, which is also position 16253 of GeneBank Accession No. NG_007506.1. The *TNFRSF1A* gene encodes on of the major receptors for TNF-alpha. This receptor can activate NF-kappaB, mediate

apoptosis, and function as a regulator of inflammation. rs1800693-G is a risk allele of MS, directing expression of a novel, soluable form of TNFSR1 that can block TNF. rs1800693-G mirrors the outcome of anti-TNF therapy in MS patients (Gregory et al 2012). The phrase "rs1800693 response allele" as used herein refers to the the "G" allele ("C" allele, in the case of the complementary strand) at the rs1800693 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has at least one rs1800693 response allele.

As used herein, "rs2863212" refers to a C/T SNP located in an intron of the human *IL-23R* gene. The rs2863212 polymorphic site is located at chromosomal postion 67685116 (build 37.3; assembly GRCh37.p5), which is position 37657034 of Contig NT_032977.9, which is also position position 57948 of GeneBank Accession No. NG_011498.1. The phrase "rs2863212 response allele" as used herein refers to the the "T" allele ("A" allele, in the case of the complementary strand) at the rs2863212 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has two rs2863212 response alleles.

As used herein "rs800292" refers to a C/T SNP located in an exon of the human *complement factor H* (*CFH)* gene (position 26093 of GeneBank Accession No. NG_007259.1). *CFH* is involved in the human complement system and is associated with dense deposit disease and age-realted macular degeneration. The rs800292 polymorphic site is located at chromosomal postion 196642233 (build 37.3; assembly GRCh37.p5), which is position 48130875 of Contig NT_004487.19. The rs800292 polymorphic site is located at position 424 of *CFH* mRNA GeneBank Accession No. NM_000186.3 and position 62 of GeneBank Accession No. NP_000177.2 When a "A" replaces a "G" at this position, the resulting missense mutation is a Val → Ile at position 52 of the *CFH* protein (position 12 of NP_000177.2). The phrase "rs800292 response allele" as used herein refers to the the "C" allele (G allele, in the case of the complementary strand) at the rs800292 polymorphic site. In some embodiments of the disclosed methods, uses, and kits, the patient has at least one rs800292 response allele. Yang et al. (2012) Mol. Vis. 18:1865-72 reports that carriers of G allele for CFH-rs800292 is higher in patients with non-infectious intermediate and posterior uveitis than in controls.

As used herein, the rs10484879 response allele, the rs4711998 response allele, the rs27689 response allele, the rs3214019 response allele, the rs72773968 response allele, the rs1937154 response allele, the rs2241046 response allele, and the rs11465770 response allele are

collectively "RA response markers." In some embodiments of the disclosed methods, uses, and kits, the patient is an RA patient that has at least one RA response marker.

As used herein, the rs28096 response allele and two rs3819024 response alleles are collectively "PsA response markers". In some embodiments of the disclosed methods, uses, and kits, the patient is a PsA patient that has at least one PsA response marker.

As used herein, the rs10484879 response allele, the rs1937154 response allele, two rs3819024 response alleles, and the rs11465770 response allele are collectively "AS response markers". In some embodiments of the disclosed methods, uses, and kits, the patient is an AS patient that has at least one AS response marker.

As used herein, the rs2241046 response allele is also referred to as the "psoriasis response marker". In some embodiments of the disclosed methods, uses, and kits, the patient is a psoriasis patient that has the psoriasis response marker.

As used herein, the rs72773968 response allele, the rs17066096 response allele, the rs2546890 response allele, the rs1800693 response allele, and the rs2863212 response allele are collectively "MS response markers." In some embodiments of the disclosed methods, uses, and kits, the patient is an MS patient that has an MS response marker.

As used herein, the rs72773968 response allele, the rs2241046 response allele, the rs11465770 response allele, the rs17482078 response allele, and the rs800292 response allele are collectively "uveitis response markers." In some embodiments of the disclosed methods, uses, and kits, the patient is a uveitis patient that has a uveitis response marker.

Some of the aforementioned response alleles are useful for the prediction of a patient's response to IL-17 antagonism for multiple AI diseases. For example, the rs72773968 response allele is useful for predicting uveitis, RA and MS patient's response to IL-17 antagonism, the rs1937154 response allele is useful for predicting both RA and AS patient's response to IL-17 antagonism, etc.. As such, each of these response alleles are members of two response marker families, e.g., the rs1937154 response allele is an RA response marker and an AS response marker.

As used herein, the phrase "AI response marker(s)" collectively refers to the uveitis response markers, RA response markers, PsA response markers, AS response markers, psoriasis response marker and MS response markers disclosed herein. In some embodiments of the disclosed methods, uses, and kits, the patient has at least one AI response marker.

As recognized by the skilled artisan, nucleic acid samples containing a particular SNP may be complementary double stranded molecules and thus reference to a particular site on the sense strand refers as well to the corresponding site on the complementary antisense strand. Similarly, reference to a particular genotype obtained for a SNP on both copies of one strand of a chromosome is equivalent to the complementary genotype obtained for the same SNP on both copies of the other strand. Thus, for example, an A/G genotype for the rs3819024 polymorphic site on one strand is equivalent to a T/C genotype for that polymorphic site on the complementary strand.

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 chromsome containing an allele of interest.

Products of the AI response markers (i.e., products of uveitis response markers, RA response markers, PsA response markers, AS response markers, psoriasis response marker and MS response markers) include nucleic acid products and polypeptide products. "Polypeptide product" refers to a polypeptide encoded by an AI response markers (i.e., products of uveitis response markers, RA response markers, PsA response markers, AS response markers, psoriasis response marker and MS response markers) and fragments thereof. "Nucleic acid product" refers to any DNA (e.g., genomic, cDNA, etc.) or RNA (e.g., pre-mRNA, mRNA, miRNA, etc.) products of an AI response markers (i.e., products of uveitis response markers, RA response markers, PsA response markers, AS response markers, psoriasis response marker and MS response markers) and fragments thereof.

An "equivalent genetic marker" refers to a genetic marker that is correlated to an allele of interest, e.g., it displays linkage disequilibrium (LD) or is in genetic linkage with the allele of interest. Equivalent genetic markers may be used to determine if a patient has an AI response marker, rather than directly interrogating a biological sample from the patient for the allele *per se*. Various programs exist to help determine LD for particular SNPs, e.g, HaploBlock (available at bioinfo.cs.technion.ac.il/haploblock/), HapMap, WGA Viewer.

The term "probe" refers to any composition of matter that is useful for specifically detecting another substance, e.g., a substance related to an AI response marker. A probe can be an oligonucleotide (including a conjugated oligonucleotide) that specifically hybridizes to a genomic sequence of an AI response marker, or a nucleic acid product of an AI response marker.

A 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, e.g., together with another primer, for amplifying a particular region within an AI response marker. Further, the probe can be an antibody that specifically binds to polypeptide products of these alleles. Further, the probe can be any composition of matter capable of detecting (e.g., binding or hybridizing) an equivalent genetic marker of an AI response marker. In preferred embodiments, the probe specifically hybridizes to a nucleic acid sequence (preferably genomic DNA) or specifically binds to a polypeptide sequence of an allele of interest. In some embodiments, the probe is at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35 nucleic acids in length.

The phrase "specifically hybridizes" is used to refer to hybrization 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.

The term "specifically binds" in the context of polypeptides is used to mean that a probe binds a given polypeptide target (e.g., a polypeptide product an AI response marker) rather than randomly binding undesireable polypeptides. However, "specifically binds" does not exclude some cross reactivity with undesireable polypeptides, as long as that cross reactivity does not

interfere with the capability of the probe to provide a a useful measure of the presence of the given polypeptide target.

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 may be used to detect the particular substance.

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

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 samples include synovial fluid, blood, blood-derived product (such as buffy coat, serum, and plasma), lymph, urine, tear, saliva, hair bulb cells, cerebrospinal fluid, buccal swabs, feces, synovial fluid, synovial cells, sputum, or tissue samples (e.g., cartilage samples). In addition, one of skill in the art would realize that some samples would be more readily analyzed following a fractionation or purification procedure, for example, isolation of DNA from whole blood.

As used herein, the phrase “different AI agent” refers to any therapeutic agent for treating a particular AI disease (i.e., uveitis, RA, PsA, AS, psoriasis or MS), provided that such agent is not an IL-17 antagonist. AI agents consist of therapeutic agents for treating RA (“RA agent”), therapeutic agents for treating PsA (“PsA agent”), therapeutic agents for treating AS (“AS agent”), therapeutic agents for treating psoriasis (“psoriasis agent”), and therapeutic agents for treating MS (“MS agent”).

Broadly speaking, an RA agent, PsA agent, and AS agent may be, *inter alia*, an immunosuppressive agent, a 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. Representative agents include cyclosporin, retinoids, corticosteroids, propionic acid derivative, acetic acid derivative, enolic acid derivatives, fenamic acid derivatives, Cox-2 inhibitors, lumiracoxib, ibuprophen, cholin magnesium salicylate, fenoprofen, salsalate, difunisal, tolmetin, ketoprofen, flurbiprofen, oxaprozin, indomethacin, sulindac, etodolac, ketorolac, nabumetone, naproxen, valdecoxib, etoricoxib, MK0966; rofecoxib, acetominophen, Celecoxib, Diclofenac, tramadol, piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam, mefanamic acid, meclofenamic acid, flufenamic acid, tolfenamic, valdecoxib, parecoxib, etodolac, indomethacin, aspirin, ibuprophen, firocoxib, methotrexate (MTX), antimalarial drugs (e.g., hydroxychloroquine and chloroquine), sulfasalazine, Leflunomide,

azathioprine, cyclosporin, gold salts, minocycline, cyclophosphamide, D-penicillamine, minocycline, auranofin, tacrolimus, myocrisin, chlorambucil, TNF alpha antagonists (e.g., TNF alpha antagonists or TNF alpha receptor antagonists), e.g., ADALIMUMAB (Humira®), ETANERCEPT (Enbrel®), INFLIXIMAB (Remicade®; TA-650), CERTOLIZUMAB PEGOL (Cimzia®; CDP870), GOLIMUMAB (Simponi®; CNTO148), ANAKINRA (Kineret®), RITUXIMAB (Rituxan®; MabThera®), ABATACEPT (Orencia®), TOCILIZUMAB (RoActemra /Actemra®), integrin antagonists (TYSABRI® (natalizumab)), IL-1 antagonists (ACZ885 (Ilaris)), Anakinra (Kineret®)), CD4 antagonists, IL-23 antagonists, IL-20 antagonists, IL-6 antagonists, BLyS antagonists (e.g., Atacicept, Benlysta®/ LymphoStat-B® (belimumab)), p38 Inhibitors, CD20 antagonists (Ocrelizumab, Ofatumumab (Arzerra®)), interferon gamma antagonists (Fontolizumab), prednisolone, Prednisone, dexamethasone, cortisol, cortisone, hydrocortisone, methylprednisolone, betamethasone, triamcinolone, beclometasome, fludrocottisone, deoxycorticosterone, aldosterone, 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 (BG-12; Biogen), 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., disclosed in WO09047356, WO2000/32773, WO2006102070, US20080227138, US20100028335, US 20030229041, WO2005003158, WO2009039175 WO2009079471, WO03106657, WO2006119062, WO08115732, WO2005/014650, WO2005/003158, WO2006/119107, WO2008/061013, WO2008/133722, WO2008/115732, US7592429, US7879322, US7744874, the contents of which are incorporated by reference herein in their entirety [preferred anti-sclerostin antibodies and antigen-binding portions thereof for use in the disclosed methods, pharmaceutical compositions, kits and uses are found in WO09047356 (equivalent to US7879322), WO06119107 (equivalent to US7872106 and US 7592429) and WO08115732 (equivalent to US7744874]), denosumab, IL-6 antagonists, CD20 antagonistis, CTLA4 antagonists, IL-8 antagonists, IL-21 antagonists, IL-22 antagonist, integrin antagonists (Tysarbri® (natalizumab)), VGEF antagnosits, CXCL antagonists, MMP antagonists, defensin antagonists, IL-1 antagonists (including IL-1 beta antagonsits), and IL-23 antagonists (e.g., receptor decoys, antagonistic antibodies, etc.). Preferred RA agents are DMARDs, such as methotrexate, and TNF alpha antagonists. Preferred AS agents are NSAIDs, DMARDS, such as sulfasalazine, and TNF alpha antagonists. Preferred PsA agents are DMARDS, such as cyclosporine, CTLA-4 blockers (e.g., CLTA4-Ig), alefacept, and TNF alpha antagonists.

Broadly speaking, psoriasis agents include, *inter alia*, topical and systemic agents, such as DMARDs, immunosuppressants, cytokine antagonists, antibiotics, and steroids. Representative psoriasis agents include, e.g., salicylic acid, coal tar, Dovonex® (calcipotriene), Taclonex® (calcipotriene and betamethasone dipropionate), Tazorec® (tazarotene), pimecrolimus, tacrolimus, Vectical® (calcitriol), Zithranol-RR® (anthralin) and topical steroids (e.g., corticosteroids), retionoids such as Acitretin (Soriatane ®), cyclosporine, methotrexate, Hydrea® (hydroxyurea), isotretinoin, mycophenolate mofetil, mycophenolic acid, sulfasalazine, 6-thioguanine, fumarates (e.g, dimethylfumarate and fumaric acid esters), azathioprine, corticosteroids, leflunomide, tacrolimus, T-cell blockers (such as Amevive® (alefacept) and Raptiva® (efalizumab), tumor necrosis factor-alpha (TNF-alpha) antagonists (such as Enbrel®

(etanercept), Humira® (adalimumab), Remicade® (infliximab) and Simponi® (golimumab)) and interleukin 12/23 blockers (such as Stelara® (ustekinumab), tasocitinib, Efalizumab, briakinumab, apremilast, mometasome, voclosporin, Ketokonazol, Neuroskin Forte, recombinant human interleukin-10, voclosporin, VX-765, MED-I545, fluphenazine decanoate, acetomuinophn, bimosiamose cream, doxycycline, vancomycin, AbGn168, Vitamin D3, RO5310074, fludarabine Calcipotriol and hydrocortisone (LEO 80190), LE80185 (Taclonex® Scalp topical suspension/Xamiol® gel), Focetria (Monovalent MF59-Adjuvanted vaccine, tgAAC94 gene therapy vector, Apremilast, Capsaicin, Psirelax, ABT-874 (anti IL-12), IDEC-114, MEDI-522, INCB018424 phosphate cream, LE29102, BMS 587101, CD 2027, CRx-191, 8-methoxypsoralen or 5- methoxypsoralen, Bicillin L-A, LY2525623, INCB018424, LY2439821, CEP-701, CC-10004, certolizumab (CZP), GW786034 (pazopanib), doxycycline Curcuminoids C3 Complex, NYC 0462, RG3421, hOKT3gamma1(Ala-Ala), BT061, teplizumab, Chondroitin sulphate, CNTO 1275, monoclonal antibody to IL-12p40 and IL-23 p40 subunits, BMS-582949, MK0873, MEDI-507, M518101, ABT-874, AMG 827, AN2728, AMG 714, AMG 139, PTH (1-34), U0267 Foam, CNTO 1275, QRX-101, CNTO 1959, LEO 22811, Imiquimod, CTLA4Ig, Alga Dunaliella Bardawil, AS101 Cream, pioglitazone, pimecrolimus, ranibizumab, Zidovudine CDP870 (Certolizumab pegol), Onercept (r-hTBP-1), ACT-128800, 4,4-dimethyl-benziso-2H-selenazine, CRx-191, CRx-197, doxercalciferol, LEO 19123 Cream (calcipotriol plus LEO 80122), LAS 41004, WBI-1001, tacrolimus, RAD001, rapamycin, rosiglitazone, pioglitazone, ABT-874, Aminopterin, AN2728, CD2027, ACT-128800, mometasone furoate, CT 327, clobetasol + LCD, BTT1023, E6201, topical vitamin B12, INCB018424 Phosphate Cream, Xamiol gel, IP10.C8, BFH772, LEO 22811, Fluphenazine, MM-093, Clobex, SCH 527123, CF101, SRT2104, BIRT2584, CC10004, Tetrathiomolybdate, CP-690,550, U0267, ASP015K, VB-201, Acitretin (also called U0279), RWJ-445380, Psoralait, Clobetasol propionate, botulinum toxin type A, alefacept, erlotinib, BCT194, Ultravate Ointment, Roflumilast, CNTO 1275, halobetasol, CTA018 cream, ILV-094, COL-121, MEDI-507, AEB071, IL-6 antagonists, CD20 antagonists, CTLA4 antagonists, IL-8 antagonists, IL-21 antagonists, IL-22 antagonist, VGEF antagonists, CXCL antagonists, MMP antagonists, defensin antagonists, IL-1beta antagonists (e.g., anakinra, canakinumab), and IL-23 antagonists (e.g., receptor decoys, antagonistic antibodies, etc.). Preferred psoriasis agents are DMARDs (e.g., MTX and

cyclosporine), IL-12/-23 antagonists (e.g., ustekinumab), CTLA-4 antagonists (e.g., CTLA4-Ig), and TNF-alpha antagonists.

Approved MS agents are: interferon-beta [IFN-β] 1a and 1b: Betaferon®/ Avonex® /Rebif® /Extavia®; glatiramer acetate: Copaxone®; natalizumab: Tysabri® (selective adhesion molecule inhibitor); mitoxantrone: Novantrone® (chemotherapeutic); fingolimod (Gilenya®/FTY720) (sphingosine-1 phosphate [S1P] receptor modulator); and teriflunomide (Aubagio®/ HMR1726). These MS agents are available to modify the disease course, treat exacerbations (relapses), reduce the accumulation of lesions, prevent nerve damage, manage symptoms, and improve function and safety. Other MS agents include masitinib, ELND002, atorvastatin, vitamin A, Cholecalciferol (Vitamin D3), alemtuzmab, Cyclophosphamide, Methylprednisolone, MIS416, RTL1000, Topamax, Duloxetine Hydrochloride (HCI), Dalfampridine, Ampyra, methylprednisolone, Daclizumab, CNTO 1275, Memantine, ATX-MS-1467, GNbAC1, SB683699 (firategrast), abatacept, L-Carnitine, Rituximab, BAF312, Inosine, Mangafodipir (Teslascan), Alemtuzumab; Fludarabine; Idebenone, levetiracetam, Androgel, Dalfampridine, MBP8298, CGP 77116, Rolipram, Ritalin, C105, Darifenacin (BAY79-4998), Lubiprostone, Dronabinol, Lithium Carbonate, donepezil, ONO-4641, LY2127399, Sativex, Myfortic® (mycophenolate sodium salt), Mycophenolate Mofetil, BIIB033, BIIB017, 3,4-diaminopyridine, ACTH, MLN1202, Fampridine (4-aminopyridine, 4-AP), BGG492, BG-12 (Biogen), pioglitazone, lamotrigine, Firategrast, Ofatumumab, Sativex®, Apo-Minocycline, epigallocatechin-gallate (Sunphenon), Nerispirdine (HP184), Tcelna, nomegestrol acetate, CTLA4Ig (e.g., RG2077), GSK1223249, CS-0777, Dexrazoxane, Flupirtine, Rivastigmine, GSK1223249, Laquinimod, F-18 FEDAA1106 (BAY85-8101), Sirolimus, EGb 761® (Tanakan®), ocrelizumab, modafinil, THC (delta-9-tetrahydrocannabiniol), cannabidiol (CBD), GW-1000-02, alfuzosin, nabilone, MOR103 (antibody to GM-CSF), rifampin, azithromycin, Zenapax, BG00012, sunphenon, dirucotide, CCI-779, IPX056, NT-KO-003, arbaclofen placarbil, ACT-128800, MEDI-551, EPO (erythropoietin, ocrelizumab, Nerispirdine, simvastatin, firategrast, HP184 (nerispirdine), tolperisone, laquinimod, ponesimod, lipoic acid, paroxetine, NU100, rhIGF-1 (CEP-151), Pleneva® (BGC20-0134), A4I Antagonist, ABT-874/Human monoclonal antibody against IL-12, atacicept, copolymer 1, riluzole, M-T412, cladribine, Colecalciferol, Adderall, CDP323, lisdexamfetamine sulfate, BG00012, Provigil, kemstro, baclofen, NBI-5788, naltrexone, MK0812, armodafinil, baminercept, hydroxyurea, Solifenacin

Succinate, tovaxin, pravastatin, and RPC1063. Preferred MS agents are IFN-β1a and 1b; glatiramer acetate; natalizumab; mitoxantrone; fingolimod; and teriflunomide.

Broadly speaking, uveitis agents include corticosteroids, such as rimexolone, loteprednol, prednisolone, triamcinolone, fluocinolone, prednisolone, solumedrol, preferably loteprednol or flucinolone. Aother uveitis agents include steroid-spering drugs such as calcineurin inhibitors (cyclosporine, tacrolimus, peimcrolimus), antimetabolities (methotrexate, myccophenolate mofetil), alkylating agents (cyclophosphamide, chlorambucil) and biologicals, (e.g., TNF antagonists (e.g., anti-TNF antibodies)). Preferred uveitis agents are corticosteroids, calcineurin inhibitors (e.g., cyclosporine), antimetabolities (e.g., MTX), alkylating agents (e.g., cyclophosphamide) and TNF alpha antagonists.

IL-17 Antagonists

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

In one embodiment, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof, e.g., secukinumab) comprises at least one immunoglobulin heavy chain variable domain (V_H) comprising 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. In one embodiment, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof, e.g., secukinumab) comprises at least one immunoglobulin light chain variable domain (V_L') comprising 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. In one embodiment, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof, e.g., secukinumab) comprises at least one immunoglobulin heavy chain variable domain (V_H) comprising 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.

In one embodiment, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion 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 (e.g., 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 immunoglobulin V_L domain comprises (e.g., 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.

In one embodiment, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion 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-X-ray	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-X-ray	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-X-ray	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-X-ray	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-X-ray	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-X-ray	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 based on the Kabat definition and as determined by the X-ray analysis, using the approach of Chothia and coworkers.

In preferred embodiments, 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. The DNA encoding the V_L of secukinumab is set forth in SEQ ID NO:9. The DNA encoding the V_H of secukinumab is set forth in SEQ ID NO:7.

In some embodiments, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof, e.g., secukinumab) 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 portion thereof, e.g., secukinumab) comprises the light chain of SEQ ID NO:15. In other embodiments, the IL-17 antagonist comprises the heavy chain of SEQ ID NO:17. In other embodiments, the IL-17 antagonist comprises the light chain 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**. The DNA encoding the light chain of secukinumab is set forth as SEQ ID NO:14. The DNA encoding the heavy chain of secukinumab is set forth as SEQ ID NO:16.

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 portion 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 portion 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, an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof) for use in the disclosed methods may comprise a derivative of the IL-17 binding molecules set forth herein by sequnence (e.g., a pegylated version of secukinumab). Alternatively, the V_H or V_L domain of an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof) for use in the disclosed methods may have V_H or V_L domains that are substantially identical to the the V_H or V_L domains set forth herein (e.g., those set forth in SEQ ID NO:8 and 10). 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/or 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. Alternatively, an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof) for use in the disclosed methods may be an amino acid sequence variant of the reference IL-17 binding molecules set forth herein. In all such cases of derivative and variants, the IL-17 antagonist is capable of inhibiting the activity of about 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.

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 portion 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.

The disclosure also includes IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding portion 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 35 days, 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 portion thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 receptor antibody or antigen-binding portion 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 IgG_1/κ 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 AI disorders.

Other preferred IL-17 antibodies for use in the disclosed methods, kits and uses are those set forth in US Patent Nos: 8,057,794; 8,003,099; 8,110,191; and 7,838,638 and US Published Patent Application Nos: 20120034656 and 20110027290.

Techniques for Assaying, Diagnostic Methods and Methods of Producing a Transmittable Form of Information

The disclosed methods are useful for the treatment, prevention, or amelioration of AI diseases, as well as predicting the likelihood of an AI disease patient's response to treatment with an IL-17 antagonist, e.g., secukinumab. These methods employ, *inter alia*, determining whether a patient has an AI response marker in a sample from the patient or determining the level of *ERAP1* expression, level of ERAP1 protein or level of ERAP1 activity.

A biological sample from the patient may be assayed for the presence of an AI response marker by any applicable conventional means, which will be selected depending on whether the

particular marker falls within an exon, an intron, a non-coding portion of mRNA or a non-conding genomic sequence.

Numerous biological samples may be used to identify the presence of alleles or proteins, the level of expression of genes or proteins, and the activity of a protein, e.g., blood, synovial fluid, buffy coat, serum, plasma, lymph, feces, urine, tear, saliva, cerebrospinal fluid, buccal swabs, sputum, or tissue. Various sources within a biological sample may be used in the disclosed methods, e.g., one may assay genomic DNA obtained from a biological sample to detect an AI response marker, or one may assay products of a an AI response marker, e.g., nucleic acid products (e.g., DNA, pre-mRNA, mRNA, micro RNAs, etc.) and polypeptide products (e.g., expressed proteins) obtained from a biological sample.

We have determined that the various SNPs of **Table 1** are useful for predicting certain patient's response to treatment by IL-17 antagonism (e.g., using secukinumab). Of the SNPs in **Table 1**, most are found in genomic DNA and introns, such that a patient's allelic status may be determined by interrogating, e.g., pre-mRNA or genomic DNA. However, the presence of the rs72773968, rs17482078 and rs800292 SNPs may be determined by assaying genomic DNA, RNA and/or protein sequence, given that these SNPs falls within exons (e.g., exonss of the *ERAP1* gene and an exon of the *CFH* gene) and produce missense amino acid changes. Accordingly, a skilled artisan will understand that one may identify whether a subject has a given AI response marker by assaying a nucleic acid product of an AI response marker, a polypeptide product of an AI response marker, or an equivalent genetic marker of an AI response marker, as appropriate for a given SNP (see **Table 1**). In preferred embodiments, a genomic sequence of an AI response marker is analyzed to determine whether a subject has an AI response marker.

As described in the Examples, the findings herein lead to the conclusion that decreased levels of *ERAP1* expression, levels of ERAP1 protein and/or levels of ERAP1 activity may be useful to predict improved response to IL-17 antagonism (e.g., secukinumab) for uveitis, psoriasis, MS, PsA, and RA patients (especially uveitis, MS, PsA and RA patients), while increased levels of *ERAP1* expression, levels of ERAP1 protein and/or levels of ERAP1 activity may be useful to predict a weaker response to IL-17 antagonism (e.g., secukinumab) for uveitis, psoriasis, MS, PsA, and RA patients (especially uveitis, MS, PsA and RA patients). Levels of *ERAP1* expression, ERAP1 protein and/or ERAP1 activity may be directly measured by various techniques disclosed herein. In addition, any *ERAP1* polymorphism (e.g., translocations,

insertions, substitutions, deletions, SNP, etc., occurring in *ERAP1* enhancers, exons, introns, promoters, 5' UTR, 3'UTR, etc.) that results in a change in the level of *ERAP1* expression, level of ERAP1 protein, and/or level of ERAP1 activity, is also expected to be useful to predict an increased or decreased likelihood of an AI patient responding to treatment with an IL-17 antagonist, e.g., secukinumab. The presence of an AI response marker or an *ERAP1* polymorphism that results in a decreased level of *ERAP1* expression, level of ERAP1 protein or level of ERAP1 activity may be detected by a variety of genotyping techniques. Typically, such genotyping techniques employ one or more oligonucleotides that are complementary to a region containing, or adjacent to, the polymorphic site (e.g., SNP) of interest. The sequence of an oligonucleotide used for genotyping a particular polymorphic site of interest is typically designed based on a context sequence or a reference sequence.

Numerous methods and devices are available to identify the presence of an AI response marker or an *ERAP1* polymorphism that results in a decreased level of *ERAP1* expression, level of ERAP1 protein or level of ERAP1 activity. DNA (genomic and cDNA) for SNP detection can be prepared from a biological sample by methods well known in the art, e.g., phenol/chloroform extraction, PUREGENE DNA® purification system from GentAS Systems (Qiagen, CA).

Detection of a DNA sequence may include examining the nucleotide(s) located at either the sense or the anti-sense strand within that region. The presence of polymorphisms in a patient may be detected from DNA (genomic or cDNA) obtained from PCR using sequence-specific probes, e.g., hydrolysis probes from Taqman, Beacons, Scorpions; or hybridization probes that detect the marker or polymorphism. For the detection of the polymorphism, sequence specific probes may be designed such that they specifically hybridize to the genomic DNA for the alleles of interest or, in some cases, an RNA of interest. Primers and probes for polymorphic sites (e.g., SNP) may be designed based on context sequences found in the NCBI SNP database available at: www.ncbi.nlm.nih.gov/snp. 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 of allele 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). Optimised allelic discrimination assays for SNPs may be purchased from Applied Biosystems (Foster City, California, USA).

Various techniques can be applied to interrogate a particular polymorphism (e.g., SNP), including, e.g., hybridization-based methods, such as dynamic allele-specific hybridization (DASH) genotyping, polymorphic site (e.g., SNP) detection through molecular beacons (Abravaya K., et al. (2003) Clin Chem Lab Med. 41:468-474), Luminex xMAP technology®, Illumina Golden Gate® technology and commercially available high-density oligonucleotide SNP arrays (e.g., the Affymetrix Human SNP 5.0 GeneChip® performs a genome-wide assay that can genotype over 500,000 human SNPs), BeadChip® kits from Illumina, e.g, Human660W-Quad and Human 1.2M-Duo); enzyme-based methods, such as restriction fragment length polymorphism (RFLP), PCR-based methods (e.g., Tetra-primer ARMS-PCR), Invader assays (Olivier M. (2005) Mutat Res. 573(1-2):103-10), various primer extension assays (incorporated into detection formats, e.g., MALDI-TOF Mass spectrometry, electrophoresis, blotting, and ELISA-like methods), TaqMan® assays, and oligonucleotide ligase assays; and other post-amplification methods, e.g., analysis of single strand conformation polymorphism (Costabile et al. (2006) Hum. Mutat. 27(12):1163-73), temperaure gradient gel electrophoresis (TGGE), denaturing high performance liquid chromatography, high-resolution melting analysis, DNA mismatch-binding protein assays (e.g., MutS protein from *Thermus aquaticus* binds different single nucleotide mismatches with different affinities and can be used in capillary electrophoresis to differentiate all six sets of mismatches), SNPLex® (proprietary SNP detecting system available from Applied Biosystems), capillary electrophoresis, mass spectrometry, and various sequencing methods, e.g., pyrosequencing and next generation sequencing, etc. Commercial kits for SNP genotyping include, e.g., Fluidigm Dynamic Array® IFCs (Fluidigm), TaqMan® SNP Genotyping Assay (Applied Biosystems), MassARRAY® iPLEX Gold (Sequenom), Type-it Fast® SNP Probe PCR Kit (Quiagen), etc.

In some embodiments, the presence of a polymorphic site (e.g., SNP) in a patient is detected using a hybridization assay. In a hybridization assay, the presence 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. In some embodiments, arrays, e.g., the MassARRAY® system (Sequenom, San Diego, California, USA) may be used to genotype a subject.

Traditional genotyping methods may also be modified for use in genotyping. Such traditional methods include, e.g., DNA amplification techniques such as PCR and variants thereof, direct sequencing, SSO hybridization coupled with the Luminex xMAP® technology, SSP typing, and 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 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 SSP™ 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.

In some cases, RNA, e.g., mature mRNA, pre-mRNA, can also be used to determine the presence of particular polymorphisms (see **Table 1**). Analysis of the sequence of mRNA transcribed from a given gene can be performed using any known method 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 AI response marker. 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 RNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated RNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. 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.

The level of expression of a gene (e.g., *ERAP1*) may be determined by measuring RNA (or reverse transcribed cDNA) levels using various techniques, e.g., a PCR-based assay, reverse-

transcriptase PCR (RT-PCR) assay, Northern blot, etc. Quantitative RT-PCR with standardized mixtures of competitive templates can also be utilized.

In some cases, the presence of a polymorphism in a patient can be determined by analyzing polypeptide products of the AI response markers (see **Table 1**). Detection of polypeptide products 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.

We also conclude that decreased levels of ERAP1 protein may be predictive of an improved response to IL-17 antagonism (e.g., secukinumab treatment) for uveitis, AS, MS, PsA, RA and psoriasis patients (preferably uveitis, MS, PsA, RA and psoriasis patients, most preferably uveitis, MS, PsA, and RA patients). We thus contemplate that testing uveitis, AS, MS, PsA, RA and psoriasis subjects (preferably uveitis, MS, PsA, RA and psoriasis patients, most preferably uveitis, MS, PsA, and RA patients) for the levels of ERAP1 protein will be useful in a variety of pharmaceutical products and methods that involve identifying individuals more likely to respond to IL-17 antagonsim therapy and in helping physicians decide whether to prescribe IL-17 antagonists (e.g., secukinumab) to a patient having uveitis, AS, MS, PsA, RA or psoriasis (preferably uveitis, MS, PsA, RA and psoriasis patients, most preferably uveitis, MS, PsA, and RA patients).

One method for detecting polypeptide products in a sample is by means of a probe that is a binding protein capable of interacting specifically with a marker protein (e.g., an antibody capable of binding ERAP1 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, 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 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 place (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 an AI response marker or ERAP1 protein 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, ^{3}H, 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 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 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 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.

The assays described above involve steps such as but not limited to, immunoblotting, immunodiffusion, immunoelectrophoresis, or immunoprecipitation. In some embodiments, an automatic analyzer is used to determine the presence of an AI response marker.

The level ERAP1 activity may be assayed by various methods disclosed in the art, e.g., via the methods set forth in Kochan et al. (2011) Proc Natl Acad Sci U S A. 108(19):7745-50.

For comparative purposes, the level of *ERAP1* expression, level of ERAP1 protein, or level of ERAP1 activity from a patient may be compared to the level of *ERAP1* expression, level

of ERAP1 protein, and level of ERAP1 activity from a control. The control may be a reference level of *ERAP1* expression, level of ERAP1 protein, or level of ERAP1 activity derived from subjects (e.g., uveitis, PsA, RA, psoriasis, RA patients) known to respond well to treatment with an IL-17 antagonist (e.g., secukinumab) or subjects known to respond poorly to treatment with an IL-17 antagonist (e.g., secukinumab), as the case may be. A control level of expression may be derived from biological samples from reference subjects (i.e., uveitis, PsA, RA, psoriasis, RA subjects known to respond well to treatment with an IL-17 antagonist (e.g., secukinumab) or subjects known to respond poorly to treatment with an IL-17 antagonist (e.g., secukinumab)), or may simply be a numerical standard (e.g., mean, median, range, [+/- standard deviation]) previously derived from reference subjects. In some embodiments the control is a reference level of *ERAP1* expression, level of ERAP1 protein, or level of ERAP1 activity derived from a subject known to respond poorly to treatment with an IL-17 antagonist and the level of *ERAP1* expression, level of ERAP1 protein, or level of ERAP1 activity (as the case may be) from the patient is compared to this control, wherein a decreased level of *ERAP1* expression, level of ERAP1 protein, or level of ERAP1 activity in the patient (relative to a control) provides an indication that the patient will have an increased likelihood of responding to treatment with the IL-17 antagonist (e.g., secukinumab). In other embodiments, the control is a reference level of *ERAP1* expression, level of ERAP1 protein, or level of ERAP1 activity derived from a subject known to respond well to treatment with an IL-17 antagonist and the level of *ERAP1* expression, level of ERAP1 protein, or level of ERAP1 activity from the patient to be treated is compared to this control, wherein a similar (e.g., statistically similar) level of *ERAP1* expression, level of ERAP1 protein, or level of ERAP1 activity in the patient (relative to a control) provides an indication that the patient will have an increased likelihood of responding to treatment with the IL-17 antagonist (e.g., secukinumab).

An AI response marker or an *ERAP1* polymorphism that results in decreased level of *ERAP1* expression, level of ERAP1 protein and/or level of ERAP1 activity can also be identified by detecting an equivalent genetic marker thereof, which can be, e.g., another polymorphic site (e.g., SNP), a microsatellite marker, another allele or other kinds of genetic polymorphisms. For example, the presence of a genetic marker on the same haplotype as an AI response marker or an *ERAP1* polymorphism, rather than an AI response marker or an *ERAP1* polymorphism *per se*, may be indicative of a patient's likelihood for responding to treatment with an IL-17 antagonist.

Two particular alleles at different loci on the same chromosome are said to be in linkage disequilibrium (LD) if the presence of one of the alleles at one locus tends to predict the presence of the other allele at the other locus. Such variants, which are referred to herein as linked variants, or proxy variants, may be any type of variant (e.g., a SNP, insertion or deletion) that is in high LD with the better response allele of interest. The candidate linked variant may be an allele of a polymorphism that is currently known. Other candidate linked variants may be readily identified by the skilled artisan using any technique well-known in the art for discovering polymorphisms.

The degree of LD between alleles of interest and a candidate linked variant may be determined using any LD measurement known in the art. LD patterns in genomic regions are readily determined empirically in appropriately chosen samples using various techniques known in the art for determining whether any two alleles (e.g., between nucleotides at different PSs) are in linkage disequilibrium (see, e.g., GENETIC DATA ANALYSIS II, Weir, Sineuer Associates, Inc. Publishers, Sunderland, MA 1996). The skilled artisan may readily select which method of determining LD will be best suited for a particular population sample size and genomic region. One of the most frequently used measures of linkage disequilibrium is r, which is calculated using the formula described by Devlin et al. (Genomics, 29(2):311-22 (1995)). “r" is the measure of how well an allele X at a first locus predicts the occurrence of an allele Y at a second locus on the same chromosome. The measure only reaches 1.0 when the prediction is perfect (e.g. X if and only if Y).

Preferably, the locus of the linked variant is in a genomic region of about 200 kilobases, more preferably 100 kilobases, more preferably about 10 kb that spans one of the polymorphic sites disclosed herein. Other linked variants are those in which the LD with the better response allele has a r2 value, as measured in a suitable reference population, of at least 0.75, more preferably at least 0.80, even more preferably at least 0.85 or at least 0.90, yet more preferably at least 0.95, and most preferably 1.0. The reference population used for this r measurement may be the general population, a population using an IL-17 antagonist, a population diagnosed with a particular condition for which the IL-17 antagonists shows efficacy (such as an RA, PsA, AS, psoriasis, or MS patient) or a population whose members are self-identified as belonging to the same ethnic group, such as Caucasian, African American, Hispanic, Latino, Native American and the like, or any combination of these categories. Preferably the reference population reflects the genetic diversity of the population of patients to be treated with the IL-17 antagonist.

Analysis of the level of *ERAP1* expression, the level of ERAP1 protein, the level of ERAP1 activity, or presence of an AI response marker or *ERAP1* polymorphism may be carried out separately or simultaneously while analyzing other genetic sequences (e.g., additional response markesr). For example, a skilled artisan may analyze a sample for more than one an AI response marker, and any combination thereof. Thus, in one aspect of the present disclosure, an array is provided to which probes that correspond in sequence to gene products, e.g., genomic DNA, cDNAs, mRNAs, cRNAs, polypeptides and fragments thereof, can be specifically hybridized or bound at a known position. As such, one may use an array to concurrently analyze a biological sample from a patient for various genomic or biochemical markers of a patient.

In performing any of the methods described herein that require determining the presence of an AI response marker or *ERAP1* polymorphism, the level of *ERAP1* expression, the level of ERAP1 protein, or the level of ERAP1 activity, such determination may be made by consulting a data repository that contains sufficient information on the patient's genetic composition to determine whether the patient has the marker of interest. Preferably, the data repository lists the genotype present (or absent) in the individual. The data repository could include the individual's patient records, a medical data card, a file (e. g., a flat ASCII file) accessible by a computer or other electronic or non-electronic media on which appropriate information or genetic data can be stored. As used herein, a medical data card is a portable storage device such as a magnetic data card, a smart card, which has an on-board processing unit and which is sold by vendors such as Siemens of Munich Germany, or a flash-memory card. If the data repository is a file accessible by a computer; such files may be located on various media, including: a server, a client, a hard disk, a CD, a DVD, a personal digital assistant such as a smart phone, Palm Pilot, a tape recorder, a zip disk, the computer's internal ROM (read-only-memory) or the internet or worldwide web. Other media for the storage of files accessible by a computer are available to skilled artisans.

Typically, once levels of *ERAP1* expression, levels of ERAP1 protein/activity, or the presence of an AI response marker or *ERAP1* polymorphism 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 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 allele are also useful in indicating the testing results. Statements regarding levels of *ERAP1* expression, levels of ERAP1 protein/activity, or the presence of an AI response marker or *ERAP1* polymorphism are also useful in indicating the testing results. These 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 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 containing levels of *ERAP1* expression, levels of ERAP1 protein/activity, or the presence of an AI response marker or *ERAP1* polymorphism in an individual. This form of information is useful for predicting the responsiveness of a patient having uveitis, RA, AS, PsA, psoriasis, or MS to treatment with an IL-17 antagonist, for selecting a course of treatment based upon that information, and for selectively treating a patient based upon that information.

Disclosed herein are methods of predicting the likelihood that a patient having an AI disease will respond to treatment with an IL-17 antagonist, comprising detecting the presence or absence of at least one AI response marker in a biological sample from the patient, wherein: a) the presence of the at least one AI response marker is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist; and b) the absence of the at least one AI response marker is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist, wherein the AI disease is selected from the group consisting of RA, PsA, AS, psoriasis, and MS, and further wherein: i) if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response

alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof; ii) if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof; iii) if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof; iv) if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele; v) if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles; and vi) if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof.

In some embodiments, the method further comprises the step of obtaining the biological sample from the patient, wherein the step of obtaining is performed prior to the step of assaying.

In some embodiments, the at least one AI response marker is detected by assaying the biological sample for a nucleic acid product of the at least one AI response marker, a polypeptide product of the at least one AI response marker, or an equivalent genetic marker of the at least one AI response marker. In some embodiments, the AI response marker is detected by assaying the biological sample for a genomic sequence of the at least one AI response marker. In some embodiments, the biological sample is selected from the group consisting of synovial fluid, blood, serum, feces, plasma, urine, tear, saliva, cerebrospinal fluid, a leukocyte sample and a tissue sample.

Disclosed herein are also various methods of predicting the likelihood that a patient having an AI disease selected from uveitis, RA, PsA, AS, psoriasis, and MS (preferably selected from uveitis, MS, RA, PsA and AS patients) will respond to treatment with an IL-17 antagonist (e.g., secukinumab), comprising detecting the level of *ERAP1* expression (e.g., mRNA, cDNA, etc.), the level of ERAP1 protein, and/or the level of ERAP1 activity in a biological sample from the

patient relative to a control; wherein a decreased level of *ERAP1* expression, decreased level of ERAP1 protein, and/or a decreased level of ERAP1 activity relative to the control is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist (e.g., secukinumab). In such an embodiment, the control is a reference level of *ERAP1* expression, level of ERAP1 protein, or level of ERAP1 activity derived from a subject known to respond poorly to treatment with an IL-17 antagonist.

Disclosed herein are also various methods of predicting the likelihood that a patient having an AI disease selected from uveitis, RA, PsA, AS, psoriasis, and MS (preferably selected from uveitis, MS, RA, PsA and AS patients) will respond to treatment with an IL-17 antagonist (e.g., secukinumab), comprising detecting the level of *ERAP1* expression (e.g., mRNA, cDNA, etc.), the level of ERAP1 protein, and/or the level of ERAP1 activity in a biological sample from the patient relative to a control; wherein a similar level of *ERAP1* expression, similar level of ERAP1 protein, or a similar level of ERAP1 activity relative to the control is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist (e.g., secukinumab). In such an embodiment, the control is a reference level of *ERAP1* expression, level of ERAP1 protein, or level of ERAP1 activity derived from a subject known to respond well to treatment with an IL-17 antagonist.

In some embodiments, the level of *ERAP1* expression, the level of ERAP1 protein, or the level of ERAP1 activity is measured by assaying the biological sample from the patient for an *ERAP1* polymorphism that results in decreased *ERAP1* expression, decreased level of ERAP1 protein, and/or decreased level of ERAP1 activity relative to the control.

In some embodiments, the presence of the at least one AI response marker, the level of *ERAP1* expression, or level of ERAP1 protein/activity is detected by a technique selected from the group consisting of Northern blot analysis, polymerase chain reaction (PCR), reverse transcription-polymerase chain reaction (RT-PCR), TaqMan-based assays, direct sequencing, dynamic allele-specific hybridization, high-density oligonucleotide SNP arrays, restriction fragment length polymorphism (RFLP) assays, primer extension assays, oligonucleotide ligase assays, analysis of single strand conformation polymorphism, temperature gradient gel electrophoresis (TGGE), denaturing high performance liquid chromatography, high-resolution melting analysis, DNA mismatch-binding protein assays, SNPLex®, capillary electrophoresis,

Southern Blot, immunoassays, immunohistochemistry, ELISA, flow cytometry, Western blot, HPLC, and mass spectrometry.

In some embodiments, the AI disease is RA. In some embodiments, the AI disease is PsA. In some embodiments, the AI disease is AS. In some embodiments, the AI disease is psoriasis. In some embodiments, the AI disease is MS. In some embodiments, the AI disease is uveitis.

In some embodiments of the disclosed methods and uses, the IL-17 antagonist is an IL-17 binding molecule or an IL-17 receptor binding molecule. In some embodiments, the IL-17 binding molecule or IL-17 receptor binding molecule is an IL-17 binding molecule. In some embodiments, the IL-17 binding molecule is an IL-17 antibody or antigen-binding portion thereof. In some embodiments of the disclosed methods and uses, the IL-17 antibody is a human antibody. In some embodiments of the disclosed methods and uses, the human IL-17 antibody is secukinumab.

Methods of Treatment and Uses of IL-17 Antagonists

The disclosed methods allow clinicians to provide a personalized therapy for AI disease (i.e., uveitis, RA, PsA, AS, MS, and psoriasis) patients, i.e., they allow determination of whether to selectively treat the patient with an IL-17 antagonist (e.g., secukinumab) or whether to selectively treat the patient with an AI agent (e.g., NSAIDs, TNF alpha antagonists, DMARDs or corticosteroids). In this way, a clinician can maximize the benefit and minimize the risk of IL-17 antagnoism in the entire population of patients afflicted with AI disease (i.e., uveitis, RA, PsA, AS, MS, and psoriasis). It will be understood that IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding portion thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 receptor antibody or antigen-binding portion thereof) are useful for the treatment, prevention, or amelioration of AI disease (i.e., uveitis, RA, PsA, AS, MS, and psoriasis) (e.g., signs and symptoms & structural changes, preventing further joint erosion, improving joint structure, etc.) as disclosed herein, particularly in patients that have an AI response marker.

The IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding portion thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 receptor antibody or antigen-binding portion 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 AI, e.g., in patients who have an AI response marker, or decreased levels of *ERAP1* expression and/or levels of ERAP1 protein/activity. 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 portion thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 receptor antibody or antigen-binding portion 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 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 portion thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 receptor antibody or antigen-binding portion thereof).

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. When a therapeutically effective amount of an IL-17 antagonist, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding portion thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 receptor antibody or antigen-binding portion 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.

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

In practicing some of 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 portion thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof) is administered to a patient, e.g., a mammal (e.g., a human). While it is understood that the disclosed methods provide for selective treatment of patients (i.e., patients having a AI selected from uveitis, RA, PsA, AS, MS and psoriasis) depending on the presence of an AI response marker, this does not preclude that, if the patient is ultimately treated with an IL-17 antagonist, such IL-17 antagonist therapy is necessarily a monotherapy. Indeed, if a patient is selected for treatment with an IL-17 antagonist, then the IL-17 antagonist (e.g., secukinumab) may be administered in accordance with the method of the disclosure either alone or in combination with other therapeutics for treating AI disease in patients, e.g., in combination with an immunosuppressive agent, a disease-modifying anti-rheumatic drug (DMARD) (e.g., MTX), a pain-control drug (e.g., tramadol or paracetamol), a steroid (e.g., prednisone), 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 therapeutics, an IL-17 antagonist may be administered either simultaneously with the other therapeutic, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering the IL-17 antagonist in combination with other therapeutics, as well as the appropriate dosages for co-delivery.

Non-steroidal anti-inflammatory drugs and pain control therapeutics useful in combination with an IL-17 antagonist, e.g., secukinumab, 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, acetominophen, 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, include, methotrexate (MTX), antimalarial drugs (e.g., hydroxychloroquine and chloroquine), sulfasalazine, leflunomide, azathioprine, cyclosporin, gold salts, minocycline, cyclophosphamide,

D-penicillamine, minocycline, auranofin, tacrolimus, myocrisin, chlorambucil. Steroids (e.g., glucocorticoids) useful in combination with an IL-17 antagonist, e.g., secukinumab, include Prednisolone, Prednisone, dexamethasone, cortisol, cortisone, hydrocortisone, methylprednisolone, betamethasone, triamcinolone, beclometasome, fludrocottisone, deoxycorticosterone, aldosterone. Other therapeutics useful in combination with an IL-17 antagonist, e.g., secukinumab, include, ADALIMUMAB (Humira®), ETANERCEPT (Enbrel®), INFLIXIMAB (Remicade®; TA-650), CERTOLIZUMAB PEGOL (Cimzia®; CDP870),GOLIMUMAB (Simponi®; CNTO148), ANAKINAS (Kineret®), RITUXIMAB (Rituxan®; MabThera®), ABATACEPT (Orencia®), TOCILIZUMAB (RoActemAS /Actemra®), integrin antagonists (TYSABRI® (natalizumab)), IL-1 antagonists (ACZ885 (Ilaris), AnakinAS (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 antagonsits, e.g., pegsunercept, etc.), BLyS antagonists (e.g., Atacicept, Benlysta®/ LymphoStat-B® (belimumab)), p38 Inhibitors, CD20 antagonists (Ocrelizumab, Ofatumumab (Arzerra®)), Interferon gamma antagonists (Fontolizumab), interferon-beta [IFN-β] 1a and 1b: Betaferon®/ Avonex® /Rebif® /Extavia®; glatiramer acetate: Copaxone®; natalizumab: Tysabri® (selective adhesion molecule inhibitor); mitoxantrone: Novantrone® (chemotherapeutic); fingolimod (Gilenya®/FTY720) (sphingosine-1 phosphate [S1P] receptor modulator); and teriflunomide (Aubagio®/ HMR1726).

An IL-17 antagonist, e.g., secukinumab, 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 (including both induction and maintenance regimens) for treating AI disease patients (i.e., patients having uveitis, RA, PsA, AS, MS or psoriasis) who have an AI response marker are provided in PCT Application No.

PCT/US2011/064307, PCT/EP2011/069476, and PCT/EP2011/067522, which are incoporated by reference herein in their entirety. Doses may be delivered based on weight, e.g., 3 mg/kg, 10 mg/kg, 15 mg/kg, or as a fixed amount, e.g., 75 mg, 150 mg, 300 mg, depending on the disease. For example, RA, PsA, AS patients may use about 75 mg, about 150 mg or 300 mg of secukinumab s.c. for maintenance dosing, while psoriasis patients typically use about 150 mg or about 300 mg secukinumab s.c. for maintenance dosing.

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 portion thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 receptor antibody or antigen-binding portion 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. Delivery of the doses may be weekly, every two weeks, every three weeks, monthly (every 4 weeks), every other month (every 8 weeks), or quarterly (every 3 months). In some embodiments, the IL-17 antagonist (e.g., secukinumab) is provided as part of an induction regimen followed by a maintenance regimen. Preferred regimens are as follows:

i.v. induction regimen (3 doses, delivered every 2 weeks) • first dose = during week 0 • second dose = during week 2 • third dose = during week 4	maintenance regimen • first monthly dose = during week 8 • every month (about 4 weeks) thereafter.
i.v. induction regimen (3 doses, delivered every 3 weeks) • first dose = during week 0 • second dose = during week 3 • third dose = during week 6	maintenance regimen • first monthly dose = during week 10 • every month (about 4 weeks) thereafter

i.v. induction regimen (3 doses, delivered every month) • first dose = during week 0 • second dose = during week 4 • third dose = during week 8	maintenance regimen • first monthly dose = during week 12 • every month (about 4 weeks) thereafter
i.v. induction regimen (2 doses, delivered every 2 weeks) • first dose = during week 0 • second dose = during week 2	maintenance regimen • first monthly dose = during week 6 • every month (about 4 weeks) thereafter
i.v. induction regimen (2 doses, delivered every 3 weeks) • first dose = during week 0 • second dose = during week 3	maintenance regimen • first monthly dose = during week 7 • every month (about 4 weeks) thereafter
i.v. induction regimen (2 doses, delivered every mongh) • first dose = during week 0 • second dose = during week	maintenance regimen • first monthly dose = during week 8 • every month (about 4 weeks) thereafter.
S.C. induction regimen (4 doses, delivered every week) • first weekly dose = during week 0 • second weekly dose = during week 1 • third weekly dose = during week 2 • fourth weekly dose = during week 3	maintenance regimen • first monthly dose = during week 7 • every month (about 4 weeks) thereafter
S.C. induction regimen (7 doses, delivered daily) • dose 1-7 = day 1-7	maintenance regimen • first monthly dose = during week 4 or 5 • every month (about 4 weeks) thereafter
S.C. induction regimen (5 doses, delivered weekly) • 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	maintenance regimen • first monthly dose = during week 8 • every month (about 4 weeks) thereafter

Table 3: Preferred dosing regimens.

Disclosed herein are methods of selectively treating a patient having an autoimmune (AI) disease, comprising either: a) selectively administering a therapeutically effective amount of an IL-17 antagonist to the patient on the basis of the patient having at least one AI response marker; or b) selectively administering a therapeutically effective amount of an AI agent to the patient on the basis of the patient not having the at least one AI response marker, wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein: i) if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof; and the AI agent is an RA agent selected from the group consisting of DMARDs and TNF alpha antagonists; ii) if the AI disease is PsA, then the at least one AI response marker is at least one

PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof; and the AI agent is a PsA agent selected from the group consisting of NSAIDs, DMARDS, CTLA-4 antagonists, alefacept, and TNF alpha antagonists; iii) if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof; and the AI agent is an AS agent selected from the group consisting of NSAIDs, DMARDS, and TNF alpha antagonists; iv) if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele; and the AI agent is a psoriasis agent selected from the group consisting of DMARDs, CTLA-4 antagonists, IL-12/-23 antagonists, and TNF-alpha antagonists; v) if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles; and the AI agent is an MS agent selected from the group consisting of IFN-b1a and 1b, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, and teriflunomide; and vi) if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof.

Disclosed herein are methods of selectively treating a patient having an AI disease with an IL-17 antagonist, comprising: a) selecting the patient for treatment with the IL-17 antagonist on the basis of a the patient having at least one AI response marker; and b) thereafter, administering a therapeutically effective amount of the IL-17 antagonist to the patient, wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein: i) if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof; ii) if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker

selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof; iii) if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof; iv) if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele; v) if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles; and vi) if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof.

Disclosed herein are methods of selectively treating a patient having an AI disease with an IL-17 antagonist, comprising: a) assaying a biological sample from the patient for at least one AI response marker selected; and b) thereafter, selectively administering to the patient either: i) a therapeutically effective amount of an IL-17 antagonist on the basis of the biological sample from the patient having the at least one AI response marker; or ii) a therapeutically effective amount of an AI agent on the basis of the biological sample from the patient not having the at least one AI response marker, wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein: i. if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof; and the AI agent is an RA agent selected from the group consisting of DMARDs and TNF alpha antagonists; ii. if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof; and the AI agent is a PsA agent selected from the group consisting of NSAIDs, DMARDS, CTLA-4 antagonists, alefacept, and TNF alpha antagonists; iii. if the AI disease is AS, then the at least

one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof; and the AI agent is an AS agent selected from the group consisting of NSAIDs, DMARDS, and TNF alpha antagonists; iv. if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele; and the AI agent is a psoriasis agent selected from the group consisting of DMARDs, CTLA-4 antagonists, IL-12/-23 antagonists, and TNF-alpha antagonists; v. if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles; and the AI agent is an MS agent selected from the group consisting of IFN-b 1a and 1b, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, and teriflunomide; and vi. if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof; and the AI agent is a uveitis agent selected from the group consisting of a corticosteroid, NSAIDs, DMARDS, and TNF alpha antagonists.

Disclosed herein are methods of selectively treating a patient having an AI disease with an IL-17 antagonist, comprising: a) assaying a biological sample from the patient for at least one AI response marker; b) thereafter, selecting the patient for treatment with the IL-17 antagonist on the basis of the biological sample from the patient having the at least one AI response marker; and c) thereafter, administering a therapeutically effective amount of the IL-17 antagonist to the patient, wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein: i) if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof; ii) if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof; iii) if the AI disease is AS, then the

at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof; iv) if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele; v) if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles; and vi) if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof.

Disclosed herein are IL-17 antagonists for use in treating a patient having an AI disease, characterized in that a therapeutically effective amount of the IL-17 antagonist is to be administered to the patient on the basis of said patient having at least one AI response marker, wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein: i) if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof; ii) if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof; iii) if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof; iv) if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele; v) if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles; and vi) if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected

from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof.

Disclosed herein are IL-17 antagonists for use in treating a patient having an AI disease, characterized in that: a) the patient is to be selected for treatment with the IL-17 antagonist on the basis of a the patient having at least one AI response marker; and b) thereafter a therapeutically effective amount of the IL-17 antagonist is to be administered to the patient wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein: i) if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof; ii) if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof; iii) if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof; iv) if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele; v) if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles; and vi) if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof.

Disclosed herein are IL-17 antagonists for use in treating a patient having an AI disease, characterized in that: a) a biological sample from the patient is to be assayed for at least one AI response marker; and b) a therapeutically effective amount of the IL-17 antagonist is to be selectively administered to the patient on the basis of the biological sample from the patient

having the at least one AI response marker, wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein: i) if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof; ii) if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof; iii) if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof; iv) if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele; v) if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles; and vi) if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof.

Disclosed herein are IL-17 antagonists for use in treating a patient having an AI disease, characterized in that: a) a biological sample from the patient is assayed for at least one AI response marker; b) the patient is selected for treatment with the IL-17 antagonist on the basis of the biological sample from the patient having the at least one AI response marker; and c) a therapeutically effective amount of the IL-17 antagonist is to be selectively administered to the patient, wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein: i) if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs1937154 response allele, an

rs2241046 response allele, an rs11465770 response allele, and combinations thereof; ii) if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof; iii) if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof; iv) if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele; v) if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles; and vi) if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof.

In some embodiments, the method further comprises the step of obtaining the biological sample from the patient, wherein the step of obtaining is performed prior to the step of assaying.

In some embodiments of the disclosed methods and uses, the at least one AI response marker is detected by assaying the biological sample for a nucleic acid product of the at least one AI response marker, a polypeptide product of the at least one AI response marker, or an equivalent genetic marker of the at least one AI response marker.

In some embodiments of the disclosed methods and uses, the at least one AI response marker is detected by assaying the biological sample for a genomic sequence of the at least one AI response marker.

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

In some embodiments of the disclosed methods and uses, the at least one AI response marker is detected by a technique selected from the group consisting of Northern blot analysis, polymerase chain reaction (PCR), reverse transcription-polymerase chain reaction (RT-PCR), TaqMan-based assays, direct sequencing, dynamic allele-specific hybridization, high-density

oligonucleotide SNP arrays, restriction fragment length polymorphism (RFLP) assays, primer extension assays, oligonucleotide ligase assays, analysis of single strand conformation polymorphism, temperature gradient gel electrophoresis (TGGE), denaturing high performance liquid chromatography, high-resolution melting analysis, DNA mismatch-binding protein assays, SNPLex®, capillary electrophoresis, Southern Blot, immunoassays, immunohistochemistry, ELISA, flow cytometry, Western blot, HPLC, and mass spectrometry.

Disclosed herein are various methods of selectively treating a patient having an AI disease selected from uveitis, RA, PsA, AS, psoriasis, and MS, comprising assaying a biological sample from the patient for the level of *ERAP1* expression (e.g., mRNA, cDNA, etc.), the level of ERAP1 protein, and/or the level of ERAP1 activity; and thereafter selectively administering a therapeutically effective amount of an IL-17 antagonist, e.g., secukinumab, to the patient if the patient has a decreased *ERAP1* expression, decreased level of ERAP1 protein, and/or a decreased level of ERAP1 activity relative to a control.

In some embodiments, the level of *ERAP1* expression, the level of ERAP1 protein, or the level of ERAP1 activity is measured by assaying the biological sample from the patient for an *ERAP1* polymorphism that results in decreased *ERAP1* expression, decreased level of ERAP1 protein, and/or decreased level of ERAP1 activity relative to the control.

In some embodiments of the disclosed methods and uses, the AI disease is RA. In some embodiments of the disclosed methods and uses, the AI disease is PsA. In some embodiments of the disclosed methods and uses, the AI disease is AS. In some embodiments of the disclosed methods and uses, the AI disease is psoriasis. In some embodiments of the disclosed methods and uses, the AI disease is MS. In some embodiments, the patient is an MS patient having relapsing remitting MS (RRMS), primary-progressive MS, secondary-progressive MS, or progressive-relapsing MS. In some embodiments, the patient is an RA patient that is a non-responder to TNF alpha antagonism and/or a DMARD (e.g, MTX), or the patient has an inadequate response to TNF alpha antagonism and/or a DMARD (e.g., MTX). In some embodiments of the disclosed methods and uses, the AI disease is uveitis. In some embodiments, the patient is a uveitis patient having non-infectious uveitis. In some embodiments, the uveitis patient has active uveitis. In some embodiments, the uveitis patient has anterior, intermediate, posterior, or pan uveitis.

In some embodiments of the disclosed methods and uses, the IL-17 antagonist is an IL-17

binding molecule or an IL-17 receptor binding molecule. In some embodiments, the IL-17 binding molecule or an IL-17 receptor binding molecule is an IL-17 binding molecule. In some embodiments, the IL-17 binding molecule is an IL-17 antibody or antigen-binding portion. In some embodiments of the disclosed methods and uses, the IL-17 antibody is a human antibody. In some embodiments of the disclosed methods and uses, the human IL-17 antibody is secukinumab.

Kits

The invention also encompasses kits for detecting an AI response marker or *ERAP1* polymorphism, or the level of *ERAP1* expression, level of ERAP1 protein or level of ERAP1 activity in a biological sample (a test sample) from a patient. Such kits can be used to predict if a patient having an AI disease selected from uveitis, RA, PsA, AS, MS and psoriasis is likely to respond (or have a higher response) to treatment with an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof). For example, the kit can comprise a probe (e.g., an oligonucleotode, antibody, labeled compound or other agent) capable of detecting an AI response marker or *ERAP1* polymorphism, or the level of *ERAP1* expression, level of ERAP1 protein or level of ERAP1 activity, products of those alleles and/or an equivalent genetic marker of those alleles in a biological sample. The kit may also comprise instructions for providing a prediction of the likelihood that the patient will respond to treatment with the IL-17 antagonist.

Probes may specifically hybridize to genomic sequences, nucleic acid products, or polypeptide products. Exemplary probes are oligonucleotides or conjugated oligonucleotides that specifically hybridizes to the response alleles of **Table 1** (e.g., from DNA, cDNA, mRNA, etc.); an antibody that is capable of differentiating between polypeptide products encoded by the disclosed alleles (e.g., an antibody that is capable of binding the CFH or ERAP1 protein); primer-extension oligonucleotides, allele-specific primers, a combination of allele-specific primers, allele-specfic probes, and primer extension primers, 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 use.

Such kits may also comprise an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen-binding portion thereof) (e.g., in liquid or lyophilized form) or a pharmaceutical composition comprising the IL-17 antagonist (described *supra).* In this way, such kits are useful in the selective treatment of AI patients using an IL-17 antagonist (e.g., secukinumab). Additionally, such kits may comprise means for administering the IL-17 antagonist (e.g., a syringe and vial, a prefilled syringe, a prefilled pen) and instructions for use. These kits may contain additional therapeutic agents (described *supra*) for treating an AI disease, e.g., for delivery in combination with the enclosed IL-17 antagonist, e.g., secukinumab.

The phrase "means for administering" is used to indicate any available implement for systemically administering a drug top 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.

General

It will be understood that, in the above-mentioned methods, therapeutic regimens, kits, uses, and pharmaceutical compositions, an artisan may analyze more than one marker. For example, it is envisioned that a clinician may choose to analyze one or many of the SNPs in **Table 1** in a single patient. In some embodiments, the haplotype of the patient may be analysed for 1, 2, 3 or more of the alleles in Table 1, e.g., all (or some) of the *ERAP1* alleles in **Table 1**. For example, a biological sample from an RA patient may be analyzed for the TGA haplotype at *ERAP1* SNPs rs27689/rs3214019/rs72773968 or a sample from a uveitis patient may be analyzed for the AT hapolotype at *ERAP1* SNPs rs72773968/rs17482078. In some embodiments, even further combinations of biomarkers may be analyzed, e.g., additional genetic markers (e.g., HLA alleles), transcription markers (e.g., mRNA/miRNA derived form blood, PBMCs, biopsies, etc.),

and protein and cellular markers (e.g., protein biomarkers in serum or feces and Th17 and Treg cells. Preferred additional biomarkers for use in the disclosed methods with the AI respose markers disclosed herein are found in WO2012059598, WO2012/082573, U.S. Provisional Application No. 61/636062 (filed April 20, 2012), and PCT/US2012/041310 (filed June 7, 2012), the contents of which are hereby incorporated herein in their entirety. A preferred *ERAP1* SNP additional marker is an rs30187 "T" allele (US Provisional Patent Application 61/636,062).

In some embodiments of the disclosed methods, treatments, regimens, uses and kits, the IL-17 binding molecule is selected from the group consisting of: a) an IL-17 antibody that binds to an epitope of IL-17 comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129; b) an IL-17 antibody that binds to an epitope of IL-17 comprising Tyr43, Tyr44, Arg46, Ala79, Asp80; c) 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; 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, 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 23 to about 35 days; and e) 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 PsA 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 preferred embodiments of the disclosed methods, treatments, regimens, uses and kits, the IL-17 antagonist is secukinumab.

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 - Secukinumab for Psoriatic Arthritis

A 24-week study in psoriatic arthritis (CAIN457A2206; n=42) was a randomized, doubleblind, placebo-controlled multi-center PoC study to assess the efficacy and safety of 2x10mg/kg i.v. secukinumab in patients with psoriatic arthritis refractory to MTX or other DMARD therapy, with or without previous TNF-α blocking therapy. Although the primary endpoint was not met, a substantial proportion of patients showed rapid and sustained improvements of clinical scores and acute phase parameters. A 52 week extension study CAIN457A2206E1 to this core study in 28 patients dosed at 3 mg/kg i.v. every 4 weeks showed no safety signal. Confirmatory phase III trials are currently ongoing.

Example 2 –Secukinumab for Ankylosing Spondylitis

CAIN457A2209 was a 28-week placebo controlled double-blind proof-of-concept study to determine the efficacy of secukinumab (2 x 10 mg/kg i.v. three weeks apart) in 30 patients with moderate to severe ankylosing spondylitis (AS) refractory to NSAID therapy with or without previous use of TNF-α blocking therapy. An additional 30 patients were recruited into Part 2 of the study and were randomized 2:2:1 into 0.1 mg/kg, 1 mg/kg and 10 mg/kg. The primary endpoint was met in Part 1, as secukinumab induced statistically significant ASAS 20% improvements compared with placebo at week 6. In Part 2, at the week 6 primaryendpoint, the Bath AS disease activity index (BASDAI) change from baseline was similar between the secukinumab 10 mg/kg and 1.0 mg/kg dose arms. Responses were induced rapidly and seen as early as week 1 after 2 x 10 mg/kg secukinumab. Reductions of spinal inflammation as measured by MRI scoring were also noted in subsets of patients. Confirmatory phase III trials are currently ongoing.

Example 3 - Secukinumab for Rheumatoid Arthritis

In a 16 week Ph IIa study in RA (CAIN457A2101; n=52) secukinumab dosed at 10 mg/kg i.v. twice, three weeks apart) showed an ACR20 response of 54% at week 6. In a 1 year Ph II study in RA (CAIN457F2201; n=237) secukinumab dosed monthly at 25, 75, 150 or 300 mg s.c. achieved ACR20 responses of up to 56% and Disease Activity Score DAS28 reductions of up to -1.4 after 16 weeks. Responses were similar in the 75, 150 and 300 mg and were maintained through week 52. In two additional 1 year Ph II studies in RA (CAIN457F2206, CAIN457F2208) ACR20 response rates at week 12 were 48% (10 mg/kg i.v. x3 q 2 weeks followed by 150 mg s.c. q 4 weeks), 55% (150 mg s.c. q week followed by 150 mg s.c. q 4 weeks) and 88% (10 mg/kg i.v. q 2 weeks x 6) respectively on secukinumab.

CAIN457F2208 was a randomized, double-blind, placebo-controlled trial, patients with RA (2010 criteria), TJC $\geq$ 6, SJC $\geq$ 6, CRP > 10 mg/L, who were biologic-naive and DMARD incomplete responders or DMARD naive, were randomized 2:1 to secukinumab 6x10 mg/kg i.v. or placebo every other week (wk). Associations of treatment effect of secukinumab vs. placebo with HLA-DRB1*04 (primary endpoint), HLA-DRB1*SE and protein markers RF and anti-CCP were assessed at wk 12 in 96 evaluable patients, using change from baseline in DAS28-CRP by ANCOVA, or ACR20 response by logistic regression.

At baseline, 46 (72%) on secukinumab and 23 (72%) on placebo were taking concomitant DMARDs; 16% were RF/anti-CCP negative. Frequency of HLA-DRB1*SE, and *04 was 72%,

and 47% respectively. ACR20 responses at wk 12 were 87.9% for secukinumab compared to 25% for placebo. Change from baseline in DAS28-CRP differed significantly as early as wk 2 and continued through wk 12. For change from baseline in DAS28-CRP, HLA-DRB1*SE status demonstrated significant associations with response to secukinumab vs. placebo (p=0.007 and 0.004, respectively). However, this association was driven by lack of placebo response in carriers vs. non-carriers. For change from baseline in DAS28-CRP, the HLA-DRB1*04 allelic group and HLA-DRB1*0401 did not demonstrate significant associations with response to secukinumab vs. placebo. Among protein markers, RF but not anti-CCP was significantly associated with both DAS28-CRP (RF p=0.022, CCP p=0.124) and ACR20 response (RF p=0.013, anti-CCP p=0.228). The small number of HLA-DRB1*SE non-carriers within the CCP/RF positive sub-cohort precluded assessment of associations in this group.

Example 4 - Secukinumab for Psoriasis

In total, 4546 patients with moderate to severe plaque psoriasis were included in studies. This included 3430 patients treated with secukinumab in 10 phase II/III studies, 2727 of whom were treated for at least 6 months and 2029 of whom were treated for at least 48 weeks. The Phase III program demonstrated secukinumab to be very effective in treating plaque psoriasis, with 300 mg being the dose that delivered the most clinically meaningful benefit to patients. The majority of patients treated with this dose achieved clear to almost clear skin, as shown by PASI 90 response and Investigator Global Assessment modified (IGA mod) 2011 0 or 1 response. More patients treated with 300 mg achieved clear/almost clear skin compared with the 150 mg dose, placebo, or with the active comparator etanercept, across all pivotal studies, and for all time points between Week 12 and Week 52.

Example 5 - Secukinumab for Relapsing Remitting MS (RRMS)

CAIN457B2201 was a Phase II randomized, multi-center, double-blind, placebo-controlled proof-of- concept study aimed at determining if secukinumab can reduce the disease activity in Relapsing-Remitting Multiple Sclerosis (RRMS), as measured by the occurrence of new active brain magnetic resonance imaging (MRI) lesions during a 24 week treatment period.

Seventy-three patients were randomized, 38 to secukinumab and 35 to placebo. Patients received 10 mg/kg secukinumab i.v. or placebo i.v. at week 0, 2, 4 and 4-weekly thereafter up to week 20. Comparing the effect of secukinumab to placebo by brain MRI, there was a 49.4%

reduction in cumulative Combined Unique Active Lesions (CUALs) (p=0.087) and a 66.6% reduction in cumulative new Gd-enhancing lesions on the week 4-24 MRIs (p=0.003). Eleven MS relapses were observed in 7 patients on secukinumab compared to 16 relapses in 11 patients on placebo, which corresponds to an aggregate annualized relapse rate of 0.4 on secukinumab and 0.7 on placebo.

Example 6: Secukinumab for Noninfectious Uveitis

A phase III clinical development program for secukinumab in uveitis patients with quiescen non-infectious posterior segment uveitis (CAIN457C2301), active non-infectious posterior segment uveitis (CAIN457C2302), and Behçet's uveitis (CAIN457C2303) was commenced in 2009 using dose regimens of 150 mg s.c. every 4 weeks (q4wk), 300 mg s.c. q4wk and 300 mg s.c every 2 weeks (q2wk). The available results did not demonstrate any significant difference between secukinumab and placebo for the primary efficacy endpoint.

Given these results, we postulated that the exposure of secukinumab may need to be higher for the treatment of uveitis. Thus, CAIN457A2208 study Cohort 6 evaluated secukinumab doses of 30 mg/kg i.v. q4wk, 10 mg/kg i.v. q2wk and 300 mg s.c. q2wk in 37 patients with active intermediate, posterior or pan-uveitis. At 8 weeks, the proportion of responders in the i.v.-treated patients was approximately double that of the s.c.-treated patients (62% in the 10 mg/kg i.v. q2wk group, 73% in the 30 mg/kg iv q4wk group, 33% in the 300 mg s.c. q2wk group). Statistically, the 30 mg/kg i.v. q4wk group met superiority criteria compared to the 300 mg s.c. q2wk dose. Therefore, further clinical studies evaluating the effects of secukinumab in non-infectious posterior uveitis are planned.

Example 7: Materials and Method for Pharmacogenetic (PG) Analysis

Example 7.1: Across-indication Pharmacogenetic (PG) study

A PG analysis was run using consented PG samples from secukinumab RA, PsA, AS (also referred to as "ASp"), psoriasis (also referred to as "Pso"), and MS trials with the obejctives to find new secukinumab response predictive genetic biomarkers in single indications and to find genetic biomarkers associating with secukinumab response across indications. **Table 4** shows sample size, dosing, efficacy endpoints, response rate, and adjusted covartiates.

Indication	Study	N in this PG study	AIN457 dosings	primary efficacy endpoint in CSP	% R in PG samples	Endpoints in this PG study	Adjusted Covariates
RA PhII	F2201	105	five s.c. of AIN457 300 or 150 or 75 or 25 mg q4wk	ACR20 at week 16	ACR20: 46%	ACR20 at week 16 ACR50 at week 16 DAS at week 16	baseline DAS, dosing
RA PoC	A2101	18	two i.v. of AIN457 10mg/kg	ACR20 at week 7	ACR20: 44%	ACR20 at week 7 ACR50 at week 7 DAS at week 7	baseline DAS, gender
PsA PoC	A2208	28	two i.v. of AIN457 10mg/kg q3wk	ACR20 at week 6	ACR20: 44%	ACR20 at week 6 ACR50 at week 6 DAS at week 6	baseline DAS
ASp PoC part 1 &2	A2209 (10 /1 mg)	31	two i.v. of AIN457 10 /1 mg/kg q3wk	ASAS20 at week 6	ASAS20: 54%	ASAS20 at week 6 ASAS40 at week 6 ASAS56 at week6 BASDI at week 6	baseline BASDI
Pso PhII	A2211 (enriched for extreme R/NR)	30	AIN457 150 mg s.c. administered at weeks 1, 2, 3, 5	PASI75 at week 12	PASI75: 50%	PASI75 at week 12 PASI at week 12	baseline PASI
MS PoC	B2201	27	AIN457 10 mg/kg at weeks 0, 2, 4, 6, 12, 16 and 20	CUAL	R: 50%	R / NR (defined by M&S)	gd_enhancing T1 lesions at screening

Table 4 – Across-indication Pharmacogenetic (PG) study design

The subjects included in the PG analysis need to satisfy the following four criteria: (1) Consented Caucasian patients treated by secukinumab; (2) Call rate >80%; (3) No gender discrepancy. Thirty extreme Responder/Non-responders were selected from the psoriasis trial to have comparable sample size with AS, PsA and MS.

Several candidate genes were selected for the PG analysis, including:

- *IL17A*: secukinumab target; plays major role in inflammatory and autoimmune diseases;
- *IL17RA/C*: receptor of IL17A;
- *IL23R*: relevant pathway, associated with multiple autoimmune diseases;
- *TRAF3IP2*: regulates IL-17 pathway; association with secukinumab response observed in PsA (International Patent Application PCT/US2012/041310, which is incorporated by reference herein in its entirety); risk factor for Pso and PsA;
- *IL12B*: strong association with secukinumab response observed in MS (unpublished data); risk factor for multiple autoimmune diseases; plays a major role in IL23R signalling and Th17 cell differentiation;
- *ERAP1*: certain alleles show strong association with secukinumab response observed in AS (US Provisional Patent Application 61/636062, which is incorporated by reference herein in its entirety); associated with AS (Evans et al. (2011) Nat Genet 43(8) 761-67, psoriasis (Strange et al. (2010) Nat Genet 42:982-990), and MS (Guerini et al. (2012) PLoS One

7(1)e29931), involved in trimming peptides for MHC presentation and cytokine receptor cleavage; risk factor for multiple autoimmune disease;

- *TNFSF15*: strong association with secukinumab response observed in Crohn's Disease and association also observed in PsA (International Patent Application PCT/US2012/041310, which is incorporated by reference herein in its entirety); plays with a major role in IL23R signalling and Th17 cell differentiation.

In order to account for multiple dosings in RA PhII trial (F2201), two parallel analyses were run in samples from: (1) Using all dosing arms (25 / 75 /150 / 300 mg) adjusting for dosing (N=105); (2) Using only high dosing groups (150 / 300 mg) (N=47). When more than one efficacy endpoints were tested, the one with with most significant p value was reported. All variants were tested individually, i.e., only 1 variant was included in the model at a time. All association tests were two-tailed, single-point tests for dominant, additive and recessive mode of inheritance. The mode of inheritance with with most significant p value was reported.

Tests for asscoiation with secukinumab response were conducted in secukinumab-treated patients were used for the genetic analysis. 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 Variants showing association with secukinumab response was also tested in placebo arm to see whether the association is specific to secukinumab.

All statistical tests were performed in SAS (SAS Institute Inc., Cary, NC, USA). Binary efficacy variables (ACR20, ACR50, ASAS20, etc) were analyzed separately using a logistic regression logistic regression tests (SAS 9.2 PROC LOGISTIC), with the efficacy endpoint as the dependent variable, SNP genotype as the independent variable (fixed effect). Continuous efficacy variable (DAS28, BASDI, etc) were analyzed separately using an ANCOVA model (SAS 9.2 PROC GLM), with the efficacy endpoint as the dependent variable, SNP genotype as the independent variable (fixed effect). Baseline disease severity, as well as other covariates that significantly associate with endpoint (sex adjusted in trial A2101, and dosage adjusted in trial F2201) were adjusted as covariantes in PG analysis.

No multiple testing adjustment was performed. The results should be considered as hypothesis generating only.

Example 7.2: Samples and Processing of Pharmacogenetic (PG) study in AIN457F2208 (RA)

HLA-DRB1*04 allelic group HLA-DRB1*SE allelic group and HLA-DRB1 position 11 V/L allelic group were assessed as primary and secondary objectives of the trial. In addition, exploratory PG analysis was performed in 53 sero-positive Secukinumab-treated patients who are Caucasians based on self-classification with the goal to identify genetic variants that may associate with the change in DAS28-CRP and ACR50 response to Secukinumab to at week 10. The following SNPs as selected from the WGS microarray data were tested as candidate genetic markers.

- Top hits for single indication in AIN457 across-indication PG analysis
  - RA (F2201): IL17A/rs10484879; IL17A/rs4711998
  - PsA (A2206): ERAP1/rs28096
  - RA (F2201 & A2101): ERAP1/rs27689; ERAP1/rs3214019
- Top hits for two or more indications in AIN457 across-indication PG analysis
  - ERAP1 / rs72773968: RA & MS
  - IL17A / rs10484879: RA & Asp
  - IL17A / rs1937154 (rs2154225 as proxy): RA & Asp
  - IL17A / rs3819024: PsA & Asp
  - IL17RA / rs2241046: RA & Pso
  - IL23R / rs11465770: RA & Asp
- Top hit from candidate SNP analysis in F2201: AFF3 /rs11676922 (risk factor of RA) (rs9653442 as proxy)
- Top 10 hits in F2201 GWAS for week 16 DAS (rs8083412 (no proxy), rs1461555, rs6585563 (no proxy), rs10736734, rs2858337 (rs5754144 as proxy), rs1366240 (rs4868644 as proxy), rs6710605 (rs4662298 as proxy), rs4971024, rs10468885 (rs4800718 as proxy), rs2069310)
- Others:
  - IL4R/rs1805010: reported to associate with Increased Th17 Cell Frequency and Poor Clinical Outcome in Rheumatoid Arthritis

- TRAF3IP2/rs33980500: reported to abolish IL-17 signaling but by doing so somehow increases Th17 and may drive Psoriasis through a non-Il-17A pathway. They claim that these patients should not respond to anti-Il-17 treatment but rather p40 or p19.
- VCAN/rs28296: p=0.00012 for association with week 16 DAS; BL expression values of VCAN correlates with AIN457 response in Asp; relevant function
- CCR6/rs3093023: reported to be associated with increased RA risk (in multiple populations) and elevated serum IL17 levels in Japanese

All association tests were two-tailed, single-point tests for an additive, dominant and recessive allelic effect using an analysis of covariance (ANCOVA) model for the change in DAS28-CRP at week 10, and a logistic regression model for ACR50 at week 10. Both models included specific genetic variant, baseline DAS28-CRP value and the first 2 principal component axes as continuous variables. No multiple testing adjustment was performed. The results should be considered as hypothesis generating only.

Example 7.3: Samples and Processing of Pharmacogenetic (PG) study in AIN457F2206 (RA)

Exploratory PG analysis was performed in 146 Caucasian RA patients in AIN457 arm in the AIN457F2206 study with the goal to find genetic variants that may associate with response to secukinumab. All are seropositive as defined by inclusion criteria of the study.

The following HLA-DRB1 allelic groups, as well as the SNPs as selected from the WGS microarray data were tested as candidate genetic markers.

- HLA-DRB1*04 allelic group
- HLA-DRB1*SE allelic group
- HLA-DRB1 position 11 V/L allelic group
- HLA-DRB1*SE allelic group major risk alleles (*0401, *0404, *0405, *0408, *1001, each allele separately, as well as pooled together as an allelic group)
- IL4R/rs1805010: reported to associate with Increased Th17 Cell Frequency and Poor Clinical Outcome in Rheumatoid Arthritis (in F2208 GG associate with better response); trend of association in F2208
- IL17A /rs3819024: association in PsA (A2206) & Asp PoC (A2209) & RA (F2208)
- IL17A /rs1937154 (rs2154225 as proxy): association in RA (F2201 and F2208) & Asp PoC (A2209)

- IL23R /rs11465770: association in RA (F2201 high doese and F2208) & Asp PoC (A2209) & Uveitis (A2208)
- IL17RA/rs2241046: association in RA (F2201) & Pso (A2211) & Uveitis (A2208)
- ERAP1/rs28096: association in PsA PoC (A2206) and RA (F2208)
- CCR6/rs3093023: reported to be associated with increased RA risk (in multiple populations) and elevated serum IL17 levels in Japanese; association in RA (F2208)
- AFF3 /rs11676922 (rs9653442 as proxy): risk factor of RA, association in RA (F2201 and F2208)
- CXCL10/rs4859588 (full LD with rs3921): change of CXCL10 associates with AIN response in F2208; This SNP was reported to associate with the development of invasive aspergillosis after allogeneic hematopoietic stem-cell transplantation (HSCT) and the disease progression of multiple sclerosis in European populations.

All association tests were two-tailed, single-point tests for an additive, dominant and recessive allelic effect using an analysis of covariance (ANCOVA) model for the change in DAS28-CRP at week12, and a logistic regression model for ACR50 at week12. Both models included specific genetic variant, baseline DAS28-CRP value and the first 2 principal component axes as fixed effects and country as random effect. The two secukinumab regimens were pooled together since the efficacy was very similar. No multiple testing adjustment was performed. The results should be considered as hypothesis generating only.

Example 7.4: Samples and Processing of Pharmacogenetic (PG) study in AIN457A2208 (uveitis)

Exploratory PG analysis was performed in Uveitis patients in AIN457 arm in the AIN457A2208 study with the goal to find genetic variants that may associate with response to secukinumab. PG samples from Cohorts 2,3,5,6 were combined for the PG analysis, with all the 10 mg/kg groups being combined as one dosing arm, and all the 30 mg/kg groups being combined as another dosing arm. The 1 mg/kg and 3 mg/kg groups were excluded since response rate is known to be very low in these arms. Parallel PG analyses was performed in (1) Caucasians only (N=26) and (2) in all races pooled together (N=36, not adjusting race).

The following SNPs observed to associate with AIN457 response in AIN457C2301 / C2302 / C2303 were tesed in first tier.

- Top hits from candidate gene analysis: rs3819025 (IL17A), rs27434 (ERAP1), rs30187(ERAP1), rs3819025 (IL17A) and rs1974226 (IL17A)
- Top hits from GWAS: rs6498026 & rs179763 (IL21R), rs1436077 & rs10412597 (NLRP8), rs654353 (RSPO2)

The following candidate SNPs were tesed in second tier.

- Top candidates for two or more indications in AIN457 across-indication PG analysis
    - ERAP1 / rs72773968: RA* & MS*
    - IL17A / rs10484879: RA** & Asp*
    - IL17A / rs1937154: RA** & Asp
    - IL17A / rs3819024: PsA & Asp*
    - IL17RA / rs2241046: RA* & Pso*
    - IL23R / rs11465770: RA * & Asp*
- Risk factors of diseases
    - risk factor for Bechet's disease: ERAP1 / rs17482078 (R725Q)
    - risk factor for anterior Uveitis: CFH-rs800292

All association tests were two-tailed, single-point tests for an additive, dominant and recessive allelic effect using an analysis of covariance (ANCOVA) model for the change in vitreous haze score from baseline (NOT the vitreous haze steps) in study eye at day 57, and a logistic regression model for response / remission (complete responders) in study eye at day 57. Both models included specific genetic variant, and baseline vitreous haze and dosing arms (10 mg/kg i.v., 30 mg/kg i.v., 300 mg s.c.) as fixed effects. SNP level p value for each endpoint was presented as minimum p values multiplied by 2 (correction of the 3 inheritance modes being tested). No multiple testing adjustment was performed. The results should be considered as hypothesis generating only.

Example 7.5: Genotyping and quality control

Blood samples from consenting patients were collected at the individual trial sites and then shipped to Covance (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.

In across-indication PG analysis, polymorphisms in *IL17A* were assessed by Sanger sequencing. The complete coding region of the gene, including all three exons, as well as the

majority of the 5' and 3' UTR regions were sequenced. PCR was performed for the regions described using unique primers carrying a universal M13 sequence tag. PCR amplification was optimized using AmpliTaq Gold Master Mix (Applied Biosystems, 43270590). PCR products were cleaned up with AMPure Xp magnetic beads (Beckman, A63882) on a Biomek FX. After cleanup, products were sequenced in both forward and reverse directions by Sanger sequencing with M13 universal primers and BigDye Terminator v3.1 (Life Technologies, 4337456). Sequencing products were cleaned up with CleanSEQ (Beckman, A29154) and then run on an Applied Biosystems 3730xl with POP-7 for sequence detection. For variant analysis, traces were aligned to reference sequences for each amplicon from NCBI using PhredPhrap (University of Washington). The traces were visually inspected for any discrepancies from canonical sequence using Consed (University of Washington, version 19.0). All sequence variations were noted and any corresponding protein coding changes characterized where possible. The final allele calls for each sample at each identified polymorphism position were captured with Polyphred (University of Washington, Version 6.18), manually QCed, and uploaded to the CGL Genotype Database.

In across-indication PG analysis, the common Hapmap SNPs with minor allele frequency (MAF)>0.01 (exons and 5kb beyond 5' and 3') as well as missense, nonsense, and frame-shift SNPs (as reported in public database HG19) of the candidate genes were selected from *IL17RA/RC, IL23R, TRAF3IP2, IL12B, ERAP1, TNFSF15*. SNPs that were reported in GWAS studies and were linked to these candidate genes were included as well. The genotyping of selected variants was done using Fluidigm SNP genotyping platform. Fluidigm SNPtype Assays was based on allele-specific PCR SNP detection chemistry, which employs tagged, allele-specific PCR primers and a common reverse primer. The assay was run in Fluidigm dynamic array, a nanofluidic system that has an integrated network of channels, chambers and valves that automatically combine the reaction of individual assay and sample. Combination of both SNPtype assay and dynamic array allows up to 9216 individual reactions to be run in a single experiment, providing high-throughput, low-cost SNP genotyping solution. A total of 640 variants were selected for genotyping. 321 variants satisfiying the following criteria were included in PG analysis: (1) Call rate in trio samples >90%; (2) Inheritance error in trio samples <=1; (3) Concordance of HapMap data >95% in trio samples (for Hapmap SNPs only); (4) Call rate in the clinical sample >80% (5) Showing polymorphism in the sample.

In AIN457F2208, HLA-DRB1 high resolution genotyping was conducted by IMGM. Each sample was analyzed using SBT (Sequencing Based Typing), SSO (Sequence Specific Oligonucleotide), SSP (Sequence Specific Primer) or combinations of those methods, without considering rare alleles that were estimated to be less frequent than 1:100,000 according to NMDP (National Marrow Donor Program) rare allele library Version 3.7.0.

In and AIN457F2206, HLA-DRB1 high resolution genotyping was determined using SSO (Sequence Specific Oligonucleotide) or combinations of SSO and SSP (Sequence Specific Primer), without considering rare alleles that were estimated to be less frequent than 1:100,000 according to NMDP (National Marrow Donor Program) rare allele library Version 3.9.0.

In AIN457F2208 and AIN457F2206, the WGS microarray data generation and quality control (QC) were conducted in this study. Single nucleotide polymorphisms (SNPs) from genomic DNA (gDNA) samples were analyzed using the Illumina HumanOMNI5Exome microarray, which contains 4,511,703 loci from HumanOMNI5 BeadChip, and 210,371 additional SNPs selected from Exome chip which were not on the commercial HumanOmni5 array. Sample quality control (QC) was conducted before genotyping, and data QC was conducted after genotyping.

In AIN457A2208, SNPs were identified by Sanger sequencing in IL17A and ERAP1. PCR was performed using unique primers carrying M13 universal sequence tags. Amplicons for each coding region were bi-directionally sequenced with universal primers and BigDye Terminator v3.1 (Applied Biosystems, 4337456). Sequencing products were cleaned up with CleanSEQ (Beckman, A29154) and run on a 3730xl Genetic Analyzer (Applied Biosystems) with POP-7 for sequence detection. Traces were aligned to reference sequences for each amplicon from NCBI using PhredPhrap (University of Washington) and were then visually inspected for discrepancies from canonical sequence using Consed (University of Washington, version 19.0). Sequence variations were noted and any corresponding coding changes characterized where possible. Genotyping was performed using TaqMan Assays-by-Design and Assays-on-Demand (Life Technologies, Carlsbad, CA). Genotyping was performed according to manufacturer's protocol PN 4332856D, using Taqman Universal Master Mix (PN 4326614), with the following exceptions: 2µl of DNA sample per reaction, for a total DNA input of 20ng, and 0.25µl of water added per reaction. PCR reactions were conducted on the GeneAmp 9700 (Applied Biosystems) using the program specified in the vendor protocol with the following

exception: standard thermal profile is used with 50 cycles, rather than 40. Endpoint reads were conducted on the ABI PRISM 7900HT Sequence Detection System, with data analysis by SNP Manager and SDS 2.2.2 (Applied Biosystems).

Example 8: **Results for PG analysis**

SNPs with nominally significant p values for association with secukinumab efficacy in at least 1 indication in the across-Indication PG analysis are summarized in **Table 1**.

Example 8.1: Association of genetic variants with secukinumab efficacy in single indications

A SNP rs10484879 has the best p value, with nominal p-value of 0.00017 in additive mode of inheritance (**Figure 1**) for association with percentage percentage ACR20 at week 16 in RA PhII trial (F2201) combining all secukinumab dosing groups adjusting for dosing. The presence of at least one 'C' allele is indicative of an increased likelihood that the patient will respond to treatment with secukinumab, and the presence of two 'C' alleles is indicative of a further increased likelihood that the patient will respond to treatment with secukinumab. Such trend of association was not observed in the placebo arm. SNP rs10484879 is in an intron of *IL17A*.

A SNP rs4711998 has nominal p-value of 0.00094 in dominant mode of inheritance (**Figure 2**) for association with reduction of DAS28 at week 16 from baseline in RA PhII trial (F2201) combining all secukinumab dosing groups adjusting for dosing. The presence of at least one 'G' allele is indicative of an increased likelihood that the patient will respond to treatment with secukinumab. Such trend of association was not observed in the placebo arm. SNP rs4711998 is near *IL17A*. A SNP rs28096 has nominal p-value of 0.00054 in dominant mode of inheritance (**Figure 3**) for association with percentage ACR50 at week 6 in secukinumab-treated PsA patients. The presence of at least one 'T' allele is indicative of an increased likelihood that the patient will respond to treatment with secukinumab. It was difficult to check for association in the placebo arm with only 3 patients having the CT/TT genotype and 1 ACR50 / ACR20 responder. SNP rs28096 is in an intron of *ERAP1*.

A SNP rs27689 has nominal p-value of 0.038 in dominant mode of inheritance for association with percentage ACR50 at week 16 in RA PhII trial (F2201) combining all secukinumab dosing groups adjusting for dosing (**Figure 4**). Such trend of association was also

observed in RA PoC trial (A2101) with nominal p-value of 0.050 (**Figure 4**). In both RA trials the presence of at least one 'T' allele is indicative of an increased likelihood that the patient will respond to treatment with secukinumab. There was no such trend of association observed in the placebo arm of F2201 trial. It was difficult to check for association in the placebo arm of A2101 trial with only 3 patients carrying 'T' allele. SNP rs27689 is in an intron of *ERAP1*.

A SNP rs3214019 has nominal p-value of 0.045 in dominant mode of inheritance for association with percentage ACR50 at week 16 in RA PhII trial (F2201) combining all secukinumab dosing groups adjusting for dosing (**Figure 5**). Such trend of association was also observed in RA PoC trial (A2101) with nominal p-value of 0.009 (**Figure 5**). In both RA trials the presence of at least one 'G' allele is indicative of an increased likelihood that the patient will respond to treatment with secukinumab. There was no such trend of association observed in the placebo arm of the F2201 trial. It was difficult to check for association in the placebo arm of the A2101 trial with only 2 patients carrying 'G' allele. SNP rs3214019 is in an intron of *ERAP1*.

A SNP rs17066096 has nominal p-value of 0.00090 in dominant mode of inheritance for association with percentage responders in MS PoC trial (B2201) (**Figure 12**). The presence of two "A" alleles is indicative of an increased likelihood that the patient will respond to treatment with secukinumab. There was no such trend of association observed in the placebo arm of the B2201 trial. SNP rs17066096 is in intergenic between IL20RA and IL22RA2.

A SNP rs2546890 has nominal p-value of 0.0049 in dominant mode of inheritance for association with percentage responders in MS PoC trial (B2201) (**Figure 13**). The presence of two "G" alleles is indicative of an increased likelihood that the patient will respond to treatment with secukinumab. There was no such trend of association observed in the placebo arm of the B2201 trial. SNP rs2546890 is in intron of *IL12B*.

A SNP rs1800693 has nominal p-value of 0.055 in dominant mode of inheritance for association with percentage responders in MS PoC trial (B2201) (**Figure 14**). The presence of at least one "G" allele is indicative of an increased likelihood that the patient will respond to treatment with secukinumab. There was no such trend of association observed in the placebo arm of the B2201 trial. SNP rs1800693 is in splicing site of *TNFRSF1A*.

A SNP rs2863212 has nominal p-value of 0.0023 in dominant mode of inheritance for association with percentage responders in MS PoC trial (B2201) (**Figure 15**). The presence of two "T' allelesis indicative of an increased likelihood that the patient will respond to treatment

with secukinumab. There was no such trend of association observed in the placebo arm of the B2201 trial. SNP rs2863212 is in intron of *IL23R*.

A SNP rs17482078 has nominal p-value of 0.037 in dominant mode of inheritance for association with percentage responders in Uveitis PoC trial combing all races (A2208) (**Figure 18**). A similar trend was observed in the subcohort of Caucasians in Uveitis PoC trial (data not shown). The presence of at least one "T' allele is indicative of an increased likelihood that the patient will respond to treatment with secukinumab. There was no placebo arm in the A2208 Uveitis trial. SNP rs17482078 is a missense SNP in *ERAP1* and a risk factor for Behcet's disease, especially in HLA-B51 carriers (Yohei Kirino et al, Nature Genetics 45:202–207, 2013).

A SNP rs800292 has nominal p-value of 0.040 in additive mode of inheritance for association with percentage remission in Uveitis PoC trial combing all races (A2208) (**Figure 19**). A similar trend was observed in the subcohort of Caucasians in Uveitis PoC trial (data not shown). The presence of at least one 'C' allele is indicative of an increased likelihood that the patient will have remission to treatment with secukinumab, and the presence of two 'C' alleles is indicative of a further increased likelihood that the patient will have remission to treatment with secukinumab. There was no placebo arm in the A2208 Uveitis trial. SNP rs800292 is a missense SNP in *CHF*, and rs800292-C is a risk factor for non-infectious intermediate and posterior uveitis. (Ming-ming Yang, et al, Molecular Vision 2012; 18:1865-1873, 2012)

Example 8.2: Association of Genetic Variants with Secukinumab Efficacy in More Than One Indication

SNP rs72773968 is coding nonsynonymous in *ERAP1*. It has nominal p-value of 0.027 in additive mode of inheritance for association with percentage ACR20 at week 16 in the RA trial F2201 combining all secukinumab dosing groups adjusting for dosing (**Figure 6**). Such trend of association was also observed for response rate in MS PoC trial (B2201) with nominal p-value of 0.023 (**Figure 6**); as well as for response rate in Uveitis PoC trial (A2208) combining all races with nominal p-value of 0.016 (**Figure 16**). A similar trend was observed in the subcohort of Caucasians (data not shown). In all three trials the presence of at least one 'A' allele is indicative of an increased likelihood that the patient will respond to treatment with secukinumab, and the presence of two 'A' alleles is indicative of a further increased likelihood that the patient will respond to treatment with secukinumab. There was no trend of association observed in the

placebo arm of F2201 and B2201. No placebo samples of the Uveitis trial A2208 are available and thus we could not test this SNP in the Uveitis placebo arm.

A SNP rs10484879 is in an intron of *IL17A*. It has nominal p-value of 0.00017 in additive mode of inheritance for association with percentage ACR20 at week 16, as well as nominal p-value of 0.006 in additive mode of inheritance for association with change of DAS28 from baseline at week 16 in the RA trial F2201 combining all secukinumab dosing groups adjusting for dosing (**Figure 7**). Such trend of association was also observed for ASAS40 at week 6 in the AS trial A2209 with nominal p-value of 0.020 (**Figure 7**). In both trials the presence of at least one 'C' allele is indicative of an increased likelihood that the patient will respond to treatment with secukinumab, and the presence of two 'C' alleles is indicative of a further increased likelihood that the patient will respond to treatment with secukinumab. There was no such trend of association observed in the placebo arm of either trial.

SNP rs1937154 is near *IL17A*. It has nominal p-value of 0.013 in additive mode of inheritance for association with percentage ACR20 at week 16 in the RA trial F2201 combining all secukinumab dosing groups adjusting for dosing (**Figure 8**). Such trend of association was also observed for ASAS5/6 at week 6 in the AS trial A2209 with nominal p-value of 0.087 (**Figure 8**). In both trials the presence of at least one 'T' allele is indicative of an increased likelihood that the patient will respond to treatment with secukinumab, and the presence of two 'T' alleles is indicative of a further increased likelihood that the patient will respond to treatment with secukinumab. It was difficult to check for association in the placebo arm due to the small sample size carrying the 'T' allele.

SNP rs3819024 is in the promoter of *IL17A*. It has nominal p-value of 0.074 in dominant mode of inheritance for association with percentage ACR20 at week 6 in the PsA trial A2206 (**Figure 9**). Such trend of association was also observed for ASAS56 at week 6 in the AS trial A2209 with nominal p-value of 0.036, as well as for ASAS40 at week 6 with nominal p-value of 0.058 (**Figure 9**). In both trials the presence of 'AA' genotype is indicative of an increase likelihood that the patient will respond to treatment with secukinumab. It was difficult to check for association in the placebo arm due to the small sample size carrying the 'G' allele.

SNP rs2241046 is in an intron of *IL17RA*. It has nominal p-value of 0.032 in additive mode of inheritance for association with change of DAS28 from baseline at week 16 in the RA trial F2201 combining secukinumab 150/300 mg dosing groups (**Figure 10**). Such trend of

association was also observed for PASI score at week 12 with nominal p-value of 0.054, as well as PASI75 at week 12 with nominal p-value of 0.017 in the psoriais A2211 trial (**Figure 10**). What's more, similar trend of association was also observed for response rate in Uveitis PoC trial (A2208) combining all races with nominal p-value of 0.006 (**Figure 17**). A similar trend was observed in the subcohort of Caucasians in Uveitis PoC trial (data not shown). In all three trials the presence of at least one 'C' allele is indicative of an increased likelihood that the patient will respond to treatment with secukinumab. There was no trend of association observed in the placebo arm of the RA trial F2201. No placebo samples from psoriasis trial A2211 or Uveitis trial A2208 were genotyped; we could not test this SNP in the psoriasis or Uveitis placebo arm.

A SNP rs11465770 has nominal p-value of 0.039 in additive mode of inheritance for association with change of DAS28 from baseline at week 16 in the RA trial F2201 combining secukinumab 150/300 mg dosing groups (**Figure 11**). Secondly, such trend of association was also observed for ASAS40 at week 6 with nominal p-value of 0.012, as well as for ASAS20 at week 6 with nominal p-value of 0.10 in the AS trial A2209 (**Figure 11**). Thirdly, such trend of association was also observed for ACR50 at week 10 in US/EU Caucasian seropositive RA patientsin in the trial F2208 with with nominal p-value of 0.0074 (**data not shown**). Forthly, such trend of association was also observed for ACR50 at week 12 in US/EU Caucasian seropositive RA patientsin in the trial F2206 with with nominal p-value of 0.0021 (**data not shown**). This trend of association was also observed for change in vitreous haze score from baseline at day 57 in Uvetis trial A2208 with with nominal p-value of 0.021 (**Figure 11**). In all these five trials the presence of 'T' allele is indicative of an increased likelihood that the patient will respond to treatment with secukinumab. There was similar trend of association observed in the placebo arm of the RA trials and AS trial. No placebo arm was available in the Uveitis trial A2208. SNP rs11465770 is in an intron of *IL23R*.

Example 9: Decreased *ERAP1* expression, levels of ERAP1 protein and/or levels of ERAP1 activity may be useful to predict improved response to IL-17 antagonism

The rs30187 "C" allele encodes a K528R variant of ERAP1 with impaired catalytic properties, and is associated with reduced incidence of AS. (Kochan et al. (2011) Proc Natl Acad Sci U S A. 108(19):7745-50). We have previously determined that AS patients having an rs30187 "T" allele, which encodes fully active ERAP1, display decreased secukinumab response, and that AS patients who carry this "T" allele typically showed higher levels of *ERAP1*

expression (US Provisional Patent Application 61/636,062, which is incorporated by reference herein in its entirety). This suggested to us that increased *ERAP1* activity and expression might predict decreased response to IL-17 antagonism for AS patients, and by correlation, that decreased *ERAP1* expression could therefore predict improved response to IL-17 antagonism for AS patients.

Here we show (**Table 1**) that various *ERAP1* SNPs are also useful in predicting uveitis, MS, PsA and RA patient's response to IL-17 antagonism (e.g., secukinumab) treatment. Most notably, we have determined that the rs17482078 "T" allele of ERAP1, a missense mutation that results in reduced ERAP1 catalytic activity, is associated with improved response to IL-17 antagonism in uveitis patients. This parallels our prior findings regarding the rs30187"C" allele in AS patients. Therefore, the data in the instant disclosure suggests that ERAP1 plays a role common to AI diseases that involve dysregulation of the IL-17 pathway (e.g., uveitis, AS, PsA, RA, MS, psoriasis, etc.). We therefore conclude that decreased levels of *ERAP1* expression, levels of ERAP1 protein and/or levels of ERAP1 activity may be useful to predict improved response to IL-17 antagonism (e.g., secukinumab) for psoriasis, uveitis, MS, PsA, and RA patients (especially uveitis, MS, PsA and RA patients), while increased levels of *ERAP1* expression, levels of ERAP1 protein and/or levels of ERAP1 activity may be useful to predict a weaker response to IL-17 antagonism (e.g., secukinumab) for psoriasis, uveitis, MS, PsA, and RA patients (especially MS, PsA and RA patients).

Conclusion

IL-17 blockade is currently being explored as a therapeutic strategy in a variety of immune-mediated inflammatory diseases, including rheumatoid arthritis, anklyosing spondylitis, uveitis, psoriasis, psoriatic arthritis and multiple sclerosis. We have identified, *inter alia*, particular genetic variants that are predictive of response to IL-17 antagonism, e.g., an IL-17 antibody, e.g., secukinumab, in various AI diseases. The predictive methods and personalized therapies disclosed herein are useful to maximize the benefit and minimize the risk of IL-17 antagonism in patients having various AI diseases by identifying those patients likely to respond prior to treatment with an IL-17 antagonist, such as secukinumab.

The findings disclosed herein could not have been predicted based solely on the fact that certain SNPs may be associated with an increased likelihood of a patient developing a particular

AI disease. For example, it is well known that 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). However, it is generally accepted that carriage of the SE does not predict whether an RA patient will respond to treatment with a TNF alpha antagonist, such as etanercept and infliximab (Emery and Dorner (2011) Ann. Rhem. Dis. 70:2063-2070; Potter et al. (2009) Ann. Rheum. Dis. 68:69-74), even though there is evidence that the SE can predict an increased likelihood that a patient will respond favorably to treatment with an IL-17 antagonist (PCT Application No. PCT/US2011/064307).

Furthermore, the findings herein could not have been predicted based solely on the particular genes in which the SNPs were studied. In the across-indication PG study, 640 variants were selected for genotyping based on their location in particular genes (e.g., *IL17A, ERAP, IL12B*, etc.). However, only 321 variants satisfied the criteria for inclusion in the PG analysis. Moreover, of those 321 variants, only 11 were considered to potentially associate with secukinumab-specific response for one or more indications. As such, one cannot predict how a patient will respond to a drug based solely on whether that patient carries an allele associated with a particular disease state or whether the patient carries a SNP in a particular gene.

WHAT IS CLAIMED IS:

1. A method of selectively treating a patient having an AI disease selected from uveitis, RA, PsA, psoriasis, and MS, comprising:

a) assaying a biological sample from the patient for the level of *ERAP1* expression, the level of ERAP1 protein, or the level ERAP1 activity; and

b) thereafter, selectively administering a therapeutically effective amount of an IL-17 antagonist to the patient if the patient has a decreased level of *ERAP1* expression, a decreased level of ERAP1 protein, or a decreased level of ERAP1 activity relative to a control.

2. A method of predicting the likelihood that a patient having an AI disease selected from uveitis, RA, PsA, psoriasis, and MS will respond to treatment with an IL-17 antagonist, comprising, assaying the level of *ERAP1* expression, the level of ERAP1 protein, or the level of ERAP1 activity in a biological sample from the patient, wherein a decreased level of *ERAP1* expression, decreased level of ERAP1 protein, or a decreased level of ERAP1 activity relative to a control is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist.

3. The method of either claim 1 or 2, wherein the step of assaying comprises assaying the biological sample from the patient for an *ERAP1* polymorphism that results in decreased *ERAP1* expression, decreased level of ERAP1 protein, and/or decreased level of ERAP1 activity relative to the control.

4. The method of claim 3, wherein the *ERAP1* polymorphism is an rs72773968 response allele, a rs17482078 response allele or a rs30187 response allele.

5. A method of selectively treating a patient having an autoimmune (AI) disease, comprising either:

a) selectively administering a therapeutically effective amount of an IL-17 antagonist to the patient on the basis of the patient having at least one AI response marker; or

b) selectively administering a therapeutically effective amount of an AI agent to the patient on the basis of the patient not having the at least one AI response marker,

wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein:

i. if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof; and the AI agent is an RA agent selected from the group consisting of DMARDs and TNF alpha antagonists;

ii. if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof; and the AI agent is a PsA agent selected from the group consisting of NSAIDs, DMARDS, CTLA-4 antagonists, alefacept, and TNF alpha antagonists;

iii. if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof; and the AI agent is an AS agent selected from the group consisting of NSAIDs, DMARDS, and TNF alpha antagonists;

iv. if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele; and the AI agent is a psoriasis agent selected from the group consisting of DMARDs, CTLA-4 antagonists, IL-12/-23 antagonists, and TNF-alpha antagonists;

v. if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693

response allele, and two rs2863212 response alleles, and combinations thereof; and the AI agent is an MS agent selected from the group consisting of IFN-β1a and 1b, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, and teriflunomide; and

vi. if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof; and the AI agent is a uveitis agent selected from the group consisting of a corticosteroid, NSAIDs, DMARDS, and TNF alpha antagonists.

6. A method of selectively treating a patient having an AI disease with an IL-17 antagonist, comprising:

a) selecting the patient for treatment with the IL-17 antagonist on the basis of a the patient having at least one AI response marker; and

b) thereafter, administering a therapeutically effective amount of the IL-17 antagonist to the patient,

wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein:

i. if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof;

ii. if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof;

iii. if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof;

iv. if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele;

v. if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles, and combinations thereof; and

vi. if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof.

7. A method of selectively treating a patient having an AI disease with an IL-17 antagonist, comprising:

a) assaying a biological sample from the patient for at least one AI response marker selected; and

b) thereafter, selectively administering to the patient either:

i. a therapeutically effective amount of an IL-17 antagonist on the basis of the biological sample from the patient having the at least one AI response marker; or

ii. a therapeutically effective amount of an AI agent on the basis of the biological sample from the patient not having the at least one AI response marker,

wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein:

i. if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof; and the AI agent is an RA agent selected from the group consisting of DMARDs and TNF alpha antagonists;

ii. if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof; and the AI agent is a PsA agent selected from the group consisting of NSAIDs, DMARDS, CTLA-4 antagonists, alefacept, and TNF alpha antagonists;

iii. if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof; and the AI agent is an AS agent selected from the group consisting of NSAIDs, DMARDS, and TNF alpha antagonists;

iv. if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele; and the AI agent is a psoriasis agent selected from the group consisting of DMARDs, CTLA-4 antagonists, IL-12/-23 antagonists, and TNF-alpha antagonists;

v. if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles, and combinations thereof; and the AI agent is an MS agent selected from the group consisting of IFN-β1a and 1b, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, and teriflunomide; and

vi. if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof; and the AI agent is a uveitis agent selected from the group consisting of a corticosteroid, NSAIDs, DMARDS, and TNF alpha antagonists.

8. A method of selectively treating a patient having an AI disease with an IL-17 antagonist, comprising:

a) assaying a biological sample from the patient for at least one AI response marker;

b) thereafter, selecting the patient for treatment with the IL-17 antagonist on the basis of the biological sample from the patient having the at least one AI response marker; and

c) thereafter, administering a therapeutically effective amount of the IL-17 antagonist to the patient,

wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein:

i. if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof;

ii. if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof;

iii. if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele,

an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof;

iv. if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele;

v. if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response allele, and combinations thereof s; and

vi. if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof.

9. A method of predicting the likelihood that a patient having an AI disease 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 AI response marker, wherein:

a) the presence of the at least one AI response marker is indicative of an increased likelihood that the patient will respond to treatment with the IL-17 antagonist; and

b) the absence of the at least one AI response marker is indicative of a decreased likelihood that the patient will respond to treatment with the IL-17 antagonist,

wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein:

i. if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154

response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof;

ii. if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof;

iii. if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof;

iv. if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele;

v. if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles, and combinations thereof; and

vi. if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof.

10. The method according to claim 9, further comprising the step of obtaining the biological sample from the patient, wherein the step of obtaining is performed prior to the step of assaying.

11. The method according to any one of claims 7-10, wherein the step of assaying comprises assaying the biological sample for a nucleic acid product of the at least one AI response marker, a polypeptide product of the at least one AI response marker, or an equivalent genetic marker of the at least one AI response marker.

12. The method according to claim 11, wherein the step of assaying comprises assaying the biological sample for a genomic sequence of the at least one AI response marker.

13. The method according to any one of claims 7-12, wherein the biological sample is selected from the group consisting of synovial fluid, blood, serum, feces, plasma, urine, tear, saliva, cerebrospinal fluid, a leukocyte sample and a tissue sample.

14. The method according to any one of claims 7-13, wherein the step of assaying comprises a technique selected from the group consisting of Northern blot analysis, polymerase chain reaction (PCR), reverse transcription-polymerase chain reaction (RT-PCR), TaqMan-based assays, direct sequencing, dynamic allele-specific hybridization, high-density oligonucleotide SNP arrays, restriction fragment length polymorphism (RFLP) assays, primer extension assays, oligonucleotide ligase assays, analysis of single strand conformation polymorphism, temperature gradient gel electrophoresis (TGGE), denaturing high performance liquid chromatography, high-resolution melting analysis, DNA mismatch-binding protein assays, SNPLex®, capillary electrophoresis, Southern Blot, immunoassays, immunohistochemistry, ELISA, flow cytometry, Western blot, HPLC, and mass spectrometry.

15. A method for producing a transmittable form of information for predicting the responsiveness of a patient having an AI disease to treatment with an IL-17 antagonist, comprising:

a) determining an increased likelihood of the patient responding to treatment with the IL-17 antagonist based on the presence of at least one AI response marker in a biological sample from the patient, wherein the AI disease is selected from the group consisting of uveitis, RA, PsA, AS, psoriasis, and MS, and further wherein:

i. if the AI disease is RA, then the at least one AI response marker is at least one RA response marker selected from the group consisting of an rs10484879 response allele, an rs4711998 response allele, two rs27689 response alleles, an rs3214019 response allele, an rs72773968 response allele, an rs10484879 response allele, an rs1937154 response allele, an rs2241046 response allele, an rs11465770 response allele, and combinations thereof;

ii. if the AI disease is PsA, then the at least one AI response marker is at least one PsA response marker selected from the group consisting of an rs28096 response allele, two rs3819024 response alleles, and a combination thereof;

iii. if the AI disease is AS, then the at least one AI response marker is at least one AS response marker selected from the group consisting of an rs10484879 response allele, an rs1937154 response allele, two rs3819024 response alleles, an rs11465770 response allele, and combinations thereof;

iv. if the AI disease is psoriasis, then the at least one AI response marker is an rs2241046 response allele;

v. if the AI disease is MS, then the at least one AI response marker is at least one MS response marker selected from the group consisting of an rs72773968 response allele, two rs17066096 response alleles, two rs2546890 response alleles, an rs1800693 response allele, and two rs2863212 response alleles, and combinations thereof; and

vi. if the AI disease is uveitis, then the at least one AI response marker is at least one uveitis response marker selected from the group consisting of an rs72773968 response allele, an rs2241046 response allele, an rs11465770 response allele, an rs17482078 response allele, an rs800292 response allele, and combinations thereof.

b) recording the result of the determining step on a tangible or intangible media form for use in transmission.

16. A method for producing a transmittable form of information for predicting the responsiveness of a patient having an AI disease selected from the group consisting of uveitis, RA, PsA, psoriasis, and MS to treatment with an IL-17 antagonist, comprising:

a) determining an increased likelihood that the patient will respond to treatment with the IL-17 antagonist based on a decreased level of *ERAP1* expression, decreased level of ERAP1 protein, or a decreased level of ERAP1 activity in a biological sample from the patient relative to a control; and

b) recording the result of the determining step on a tangible or intangible media form for use in transmission.

17. The method or use according to any of the above claims, wherein the AI disease is RA.

18. The method or use according to any of the above claims, wherein the AI disease is PsA.

19. The method or use according to any of the above claims, wherein the AI disease is psoriasis.

20. The method or use according to any of the above claims, wherein the AI disease is MS.

21. The method or use according to any of the above claims, wherein the AI disease is uveitis.

22. The method or use according to any of claims 5-15, wherein the AI disease is AS.

23. The method or use 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.

24. The method or use according to claim 23, wherein the IL-17 binding molecule or an IL-17 receptor binding molecule is an IL-17 binding molecule.

25. The method or use according to claim 24, wherein the IL-17 binding molecule is an IL-17 antibody or antigen-binding portion thereof.

26. The method or use according to claim 25, wherein the IL-17 antibody or antigen-binding portion thereof is an IL-17 antibody selected from the group consisting of:

a) an IL-17 antibody that binds to an epitope of IL-17 comprising Leu74, Tyr85, His86, Met87, Asn88, Val124, Thr125, Pro126, Ile127, Val128, His129;

b) an IL-17 antibody that binds to an epitope of IL-17 comprising Tyr43, Tyr44, Arg46, Ala79, Asp80;

c) 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;

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, wherein the IL-17 antibody has a K_D of about 100-200 pM, and wherein the IL-17 antibody has an *in vivo* half-life of about 23 to about 35 days; and

e) 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 PsA 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.

27. The method or use according to claim 26, wherein the IL-17 antibody is a human antibody, preferably a monoclonal human antibody.

28. The method or use according to claim 27, wherein the human IL-17 antibody is secukinumab.

Fig. 1

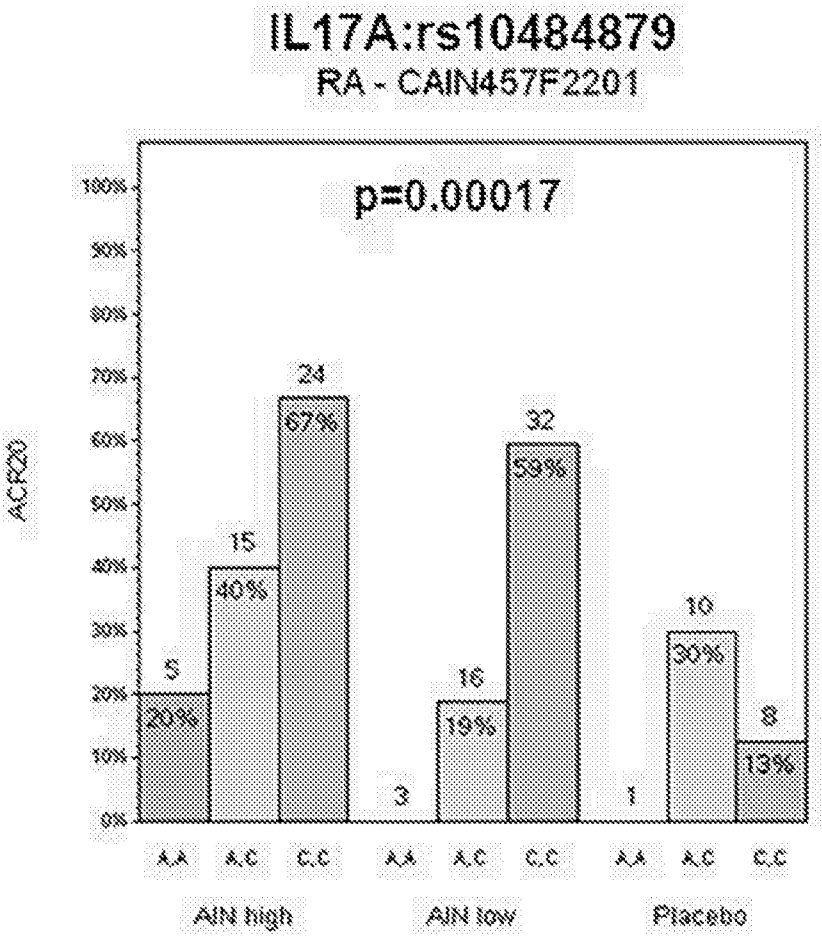

IL17A:rs10484879
RA - CAIN457F2201
p=0.00017
ACR20
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
5
20%
15
40%
24
67%
3
16
19%
32
59%
1
10
30%
8
13%
A,A
A,C
C,C
AIN high
AIN low
Placebo

Fig. 2

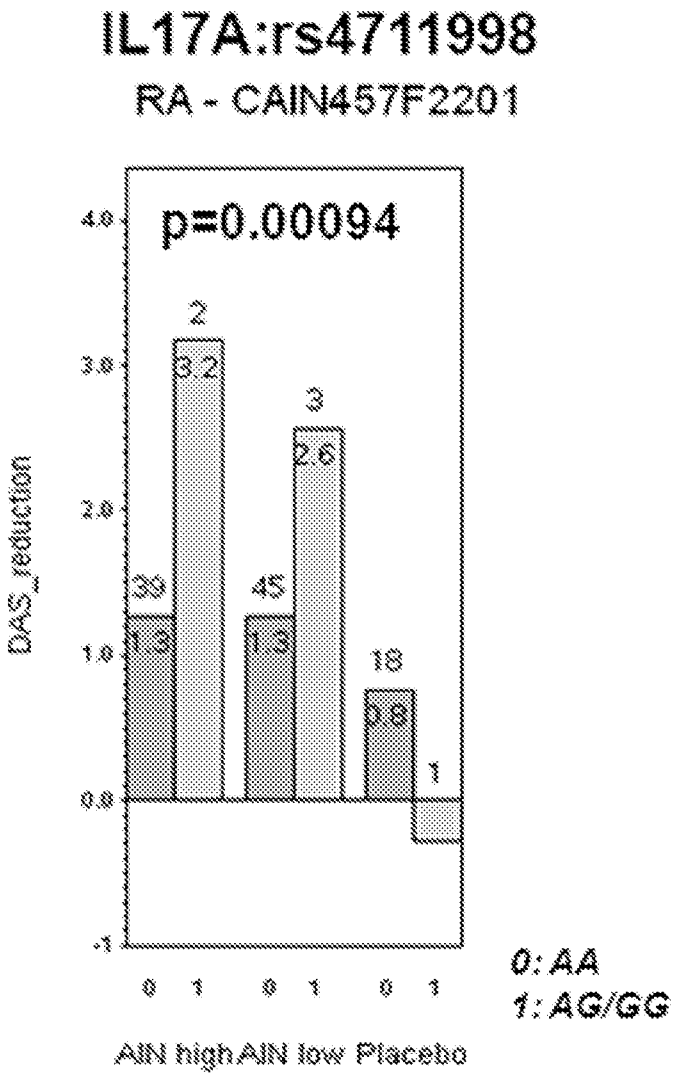

IL17A:rs4711998
RA - CAIN457F2201
p=0.00094
DAS_reduction
4.0
3.0
2.0
1.0
0.0
-.1
2
3.2
3
2.6
39
1.3
45
1.3
18
0.8
1
0 1 0 1 0 1
AIN high AIN low Placebo
0: AA
1: AG/GG

Fig. 3

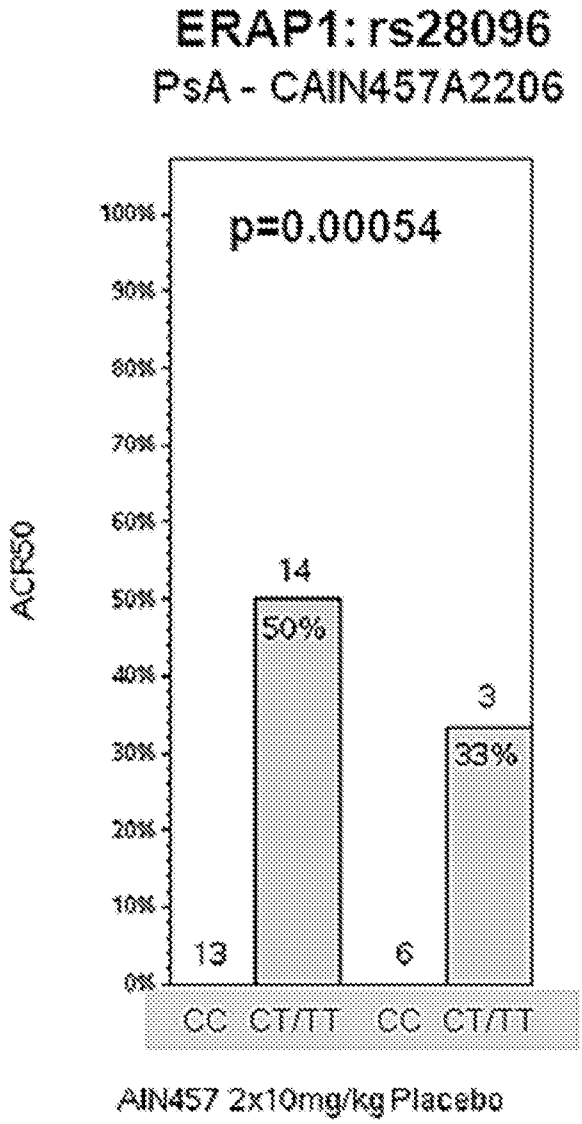
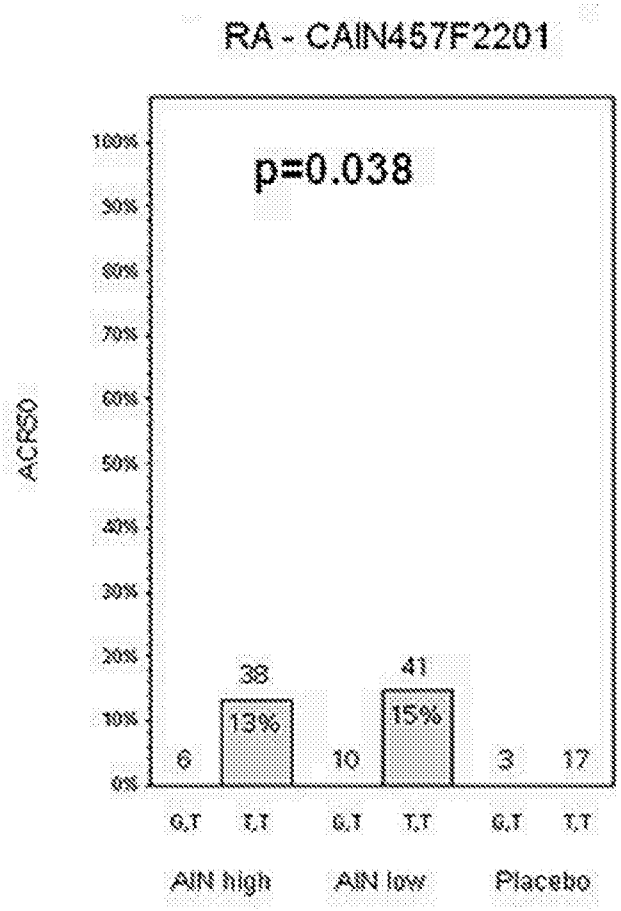

ERAP1: rs28096
PsA - CAIN457A2206
p=0.00054
ACR50
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
14
50%
3
33%
13
6
CC
CT/TT
CC
CT/TT
AIN457 2x10mg/kg
Placebo

Fig. 4

A


RA - CAIN457F2201
p=0.038
ACR50
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
6
38
13%
10
41
15%
3
17
G,T
T,T
G,T
T,T
G,T
T,T
AIN high
AIN low
Placebo

B

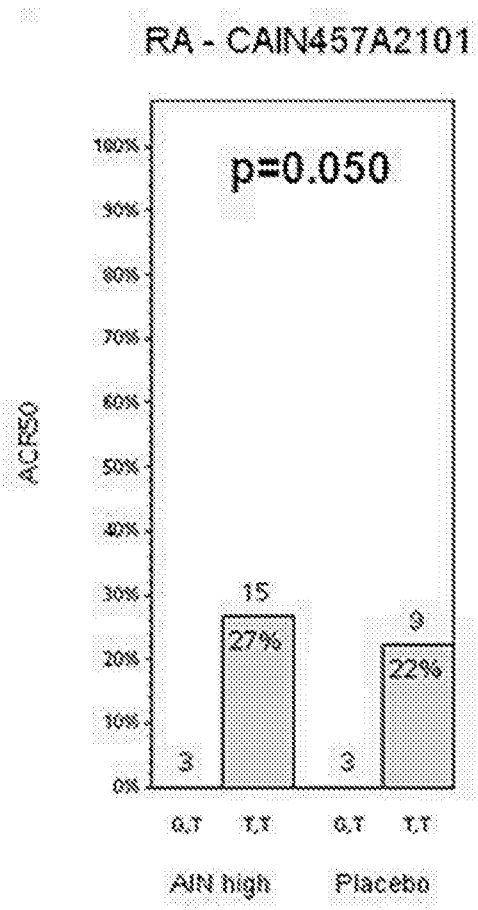
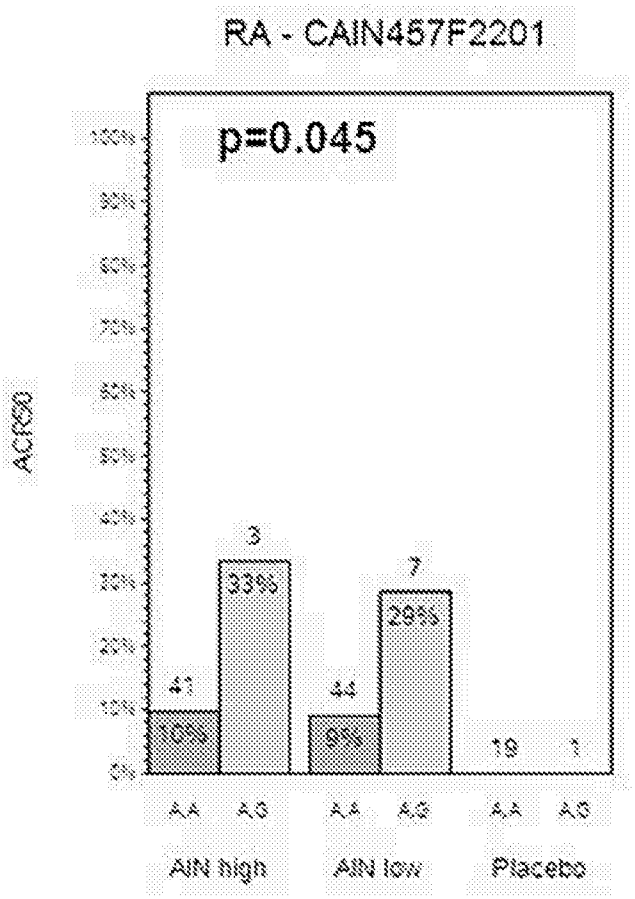

RA - CAIN457A2101
p=0.050
ACR50
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
3
15
27%
3
9
22%
G,T
T,T
G,T
T,T
AIN high
Placebo

Fig. 5

A


RA - CAIN457F2201
p=0.045
ACR50
100%
80%
60%
40%
20%
0%
41
16%
3
33%
44
9%
7
29%
19
1
A,A
A,G
A,A
A,G
A,A
A,G
AIN high
AIN low
Placebo

B

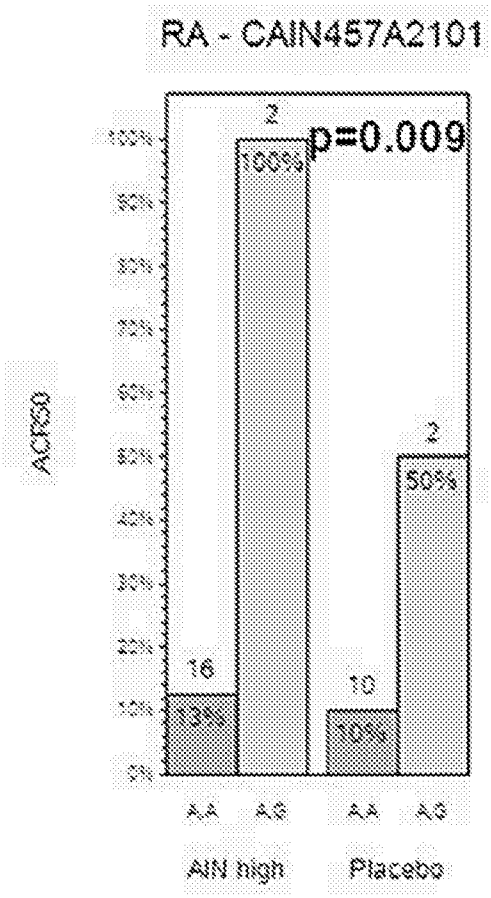
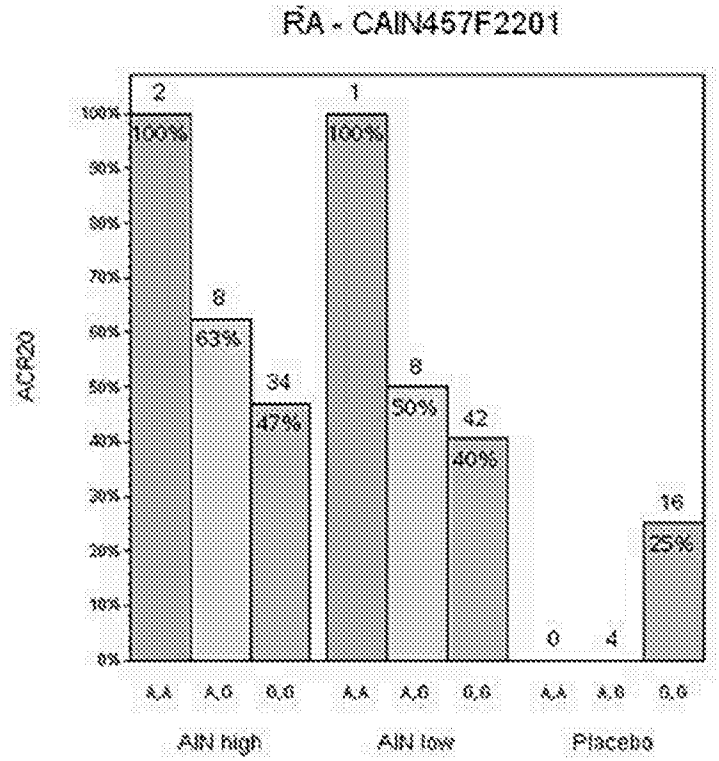

RA - CAIN457A2101
p=0.009
ACR50
100%
80%
60%
40%
20%
0%
16
13%
2
100%
10
10%
2
50%
A,A
A,G
A,A
A,G
AIN high
Placebo

Fig. 6

A


RA - CAIN457F2201
ACR20
2
100%
8
63%
34
47%
1
100%
8
50%
42
40%
0
4
16
25%
AIN high
AIN low
Placebo

B

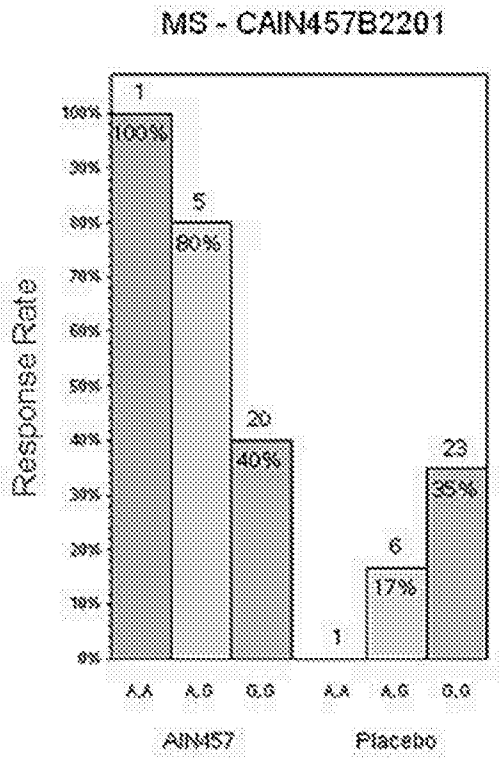

MS - CAIN457B2201
Response Rate
1
100%
5
80%
20
40%
1
6
17%
23
35%
AIN457
Placebo

Fig. 7

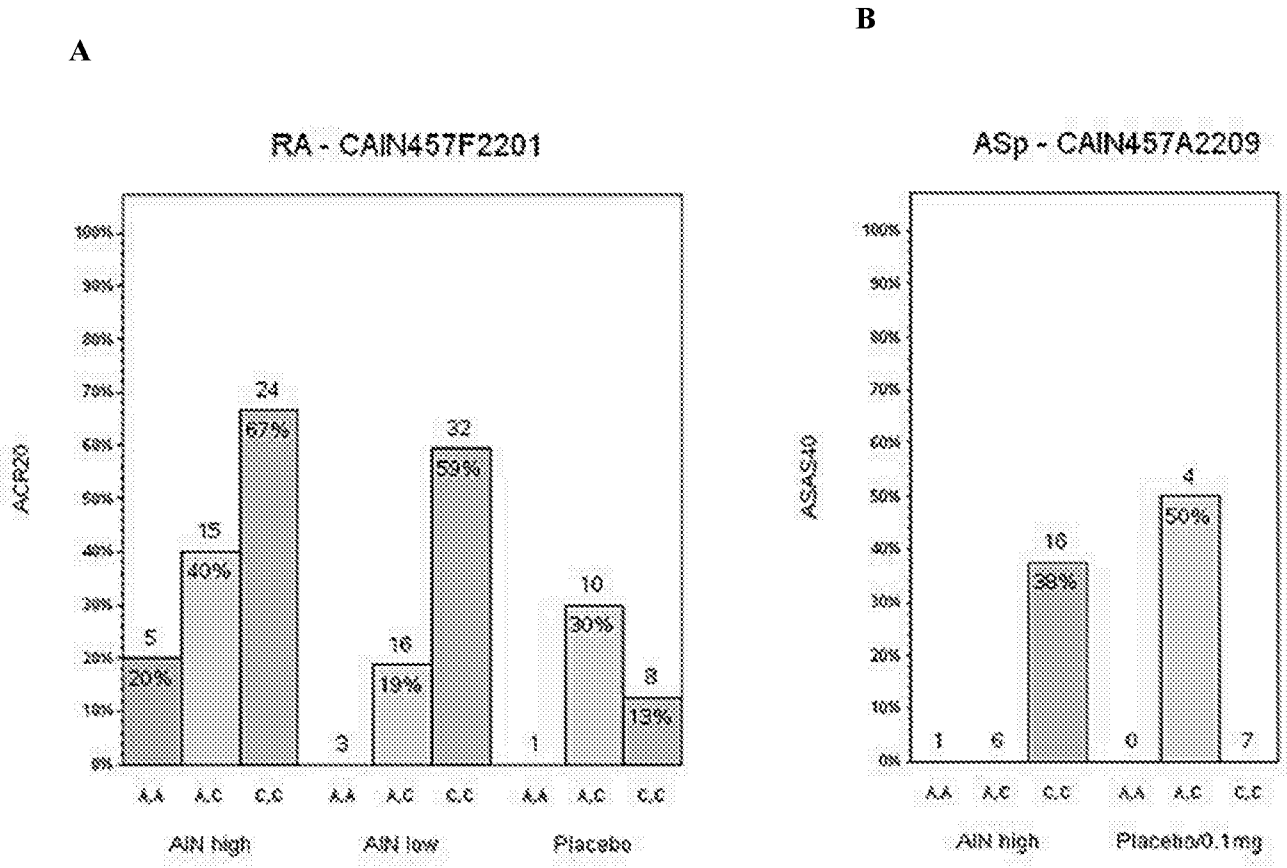
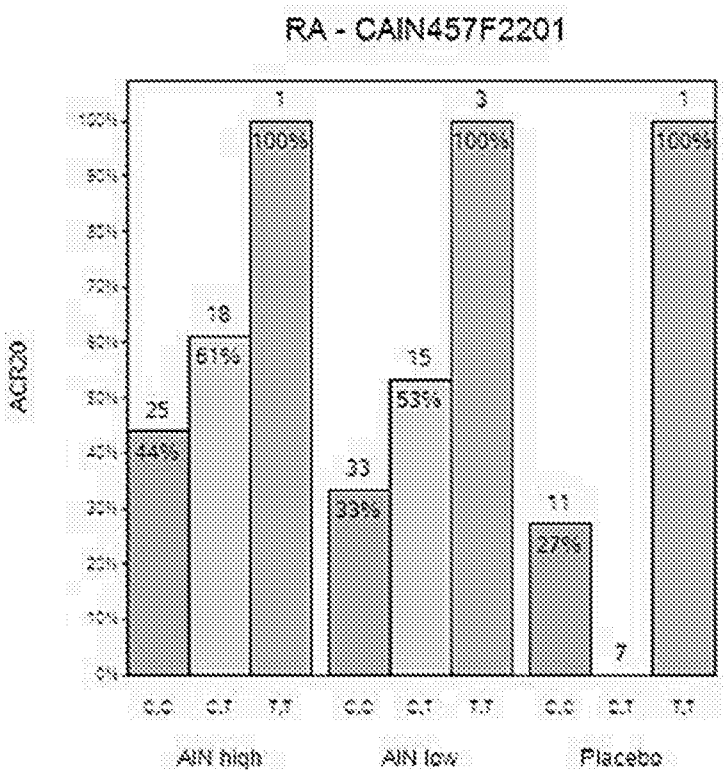

A
RA - CAIN457F2201
ACR20
5
20%
15
40%
24
67%
3
16
19%
32
53%
1
10
30%
8
13%
A,A
A,C
C,C
AIN high
AIN low
Placebo
B
ASp - CAIN457A2209
ASAS40
1
6
16
38%
0
4
50%
7
AIN high
Placebo0.1mg

Fig. 8

A


RA - CAIN457F2201
ACR20
25
44%
18
61%
1
100%
33
33%
15
53%
3
100%
11
27%
7
1
100%
AIN high
AIN low
Placebo

B

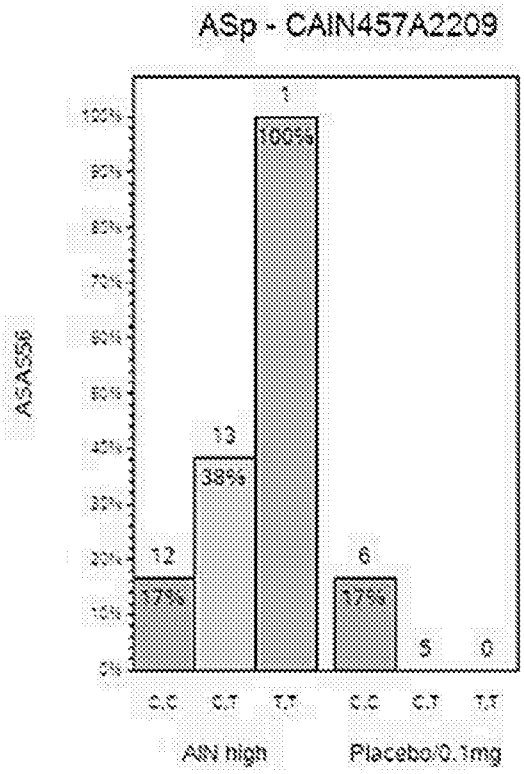

ASp - CAIN457A2209
ASAS50
12
13
38%
1
100%
6
17%
5
0
AIN high
Placebo/0.1mg

Fig. 9

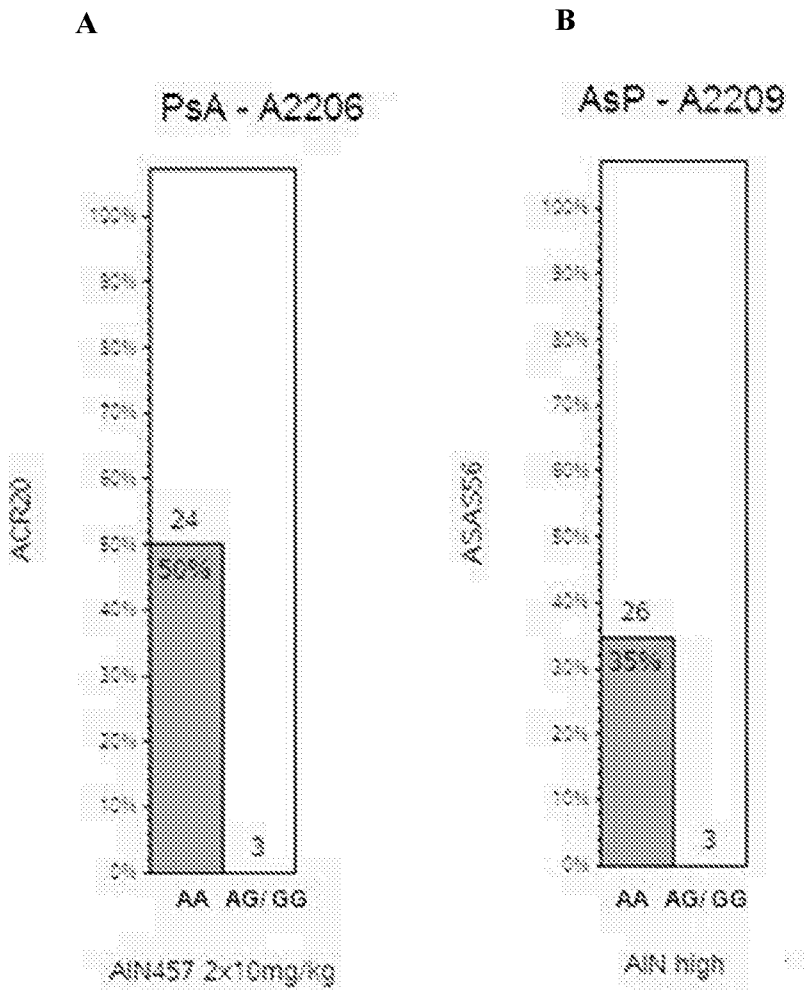

A
PsA - A2206
ACR20
24
3
AA
AG/GG
AIN457 2x10mg/kg
B
AsP - A2209
ASAS56
26
3
AA
AG/GG
AIN high

Fig. 10

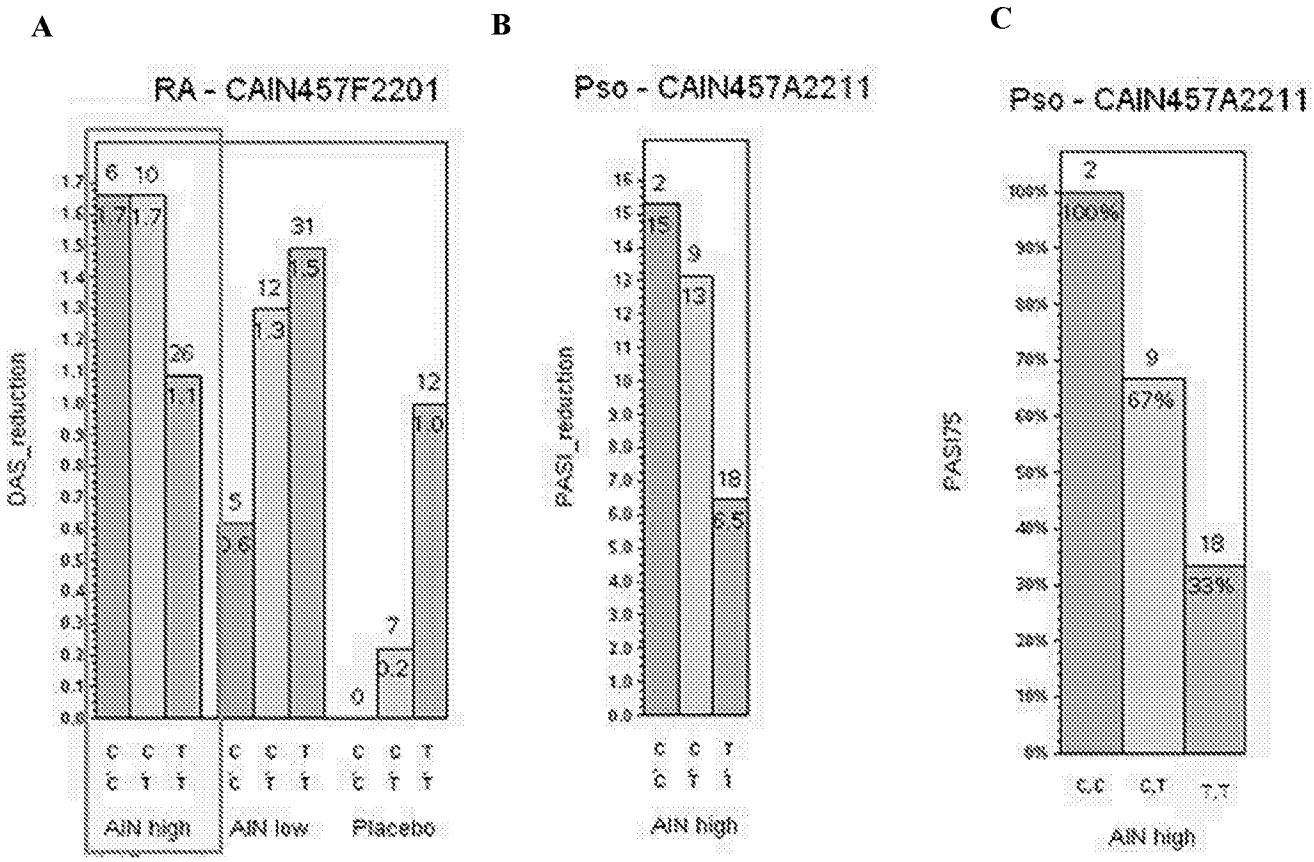
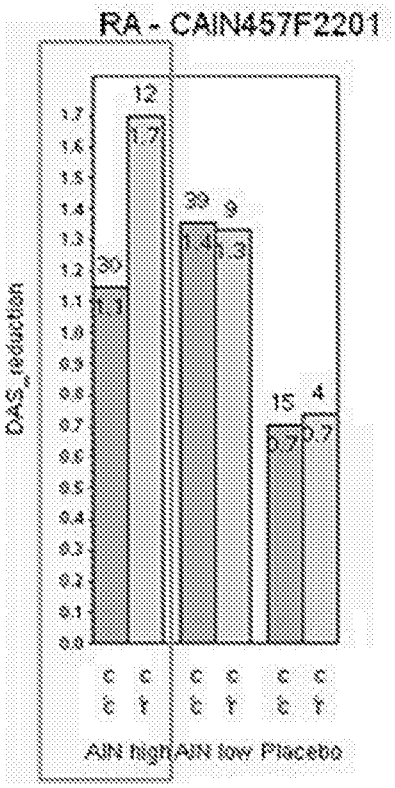
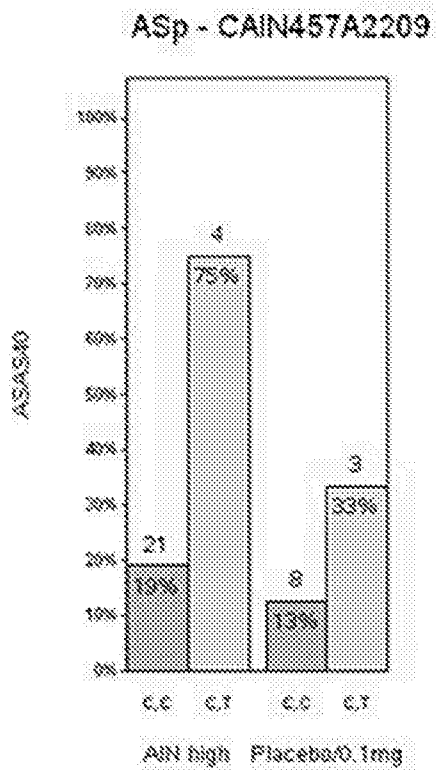

A
RA - CAIN457F2201
DAS_reduction
6
10
26
5
31
12
0
7
12
C C T
C T T
AIN high
AIN low
Placebo
B
Pso - CAIN457A2211
PASI_reduction
2
9
18
AIN high
C
Pso - CAIN457A2211
PASI75
2
100%
9
67%
18
33%
C,C
C,T
T,T
AIN high

Fig. 11

A


RA - CAIN457F2201
DAS_reduction
AIN high
AIN low
Placebo

B


ASp - CAIN457A2209
ASAS40
AIN high
Placebo/0.1mg

C

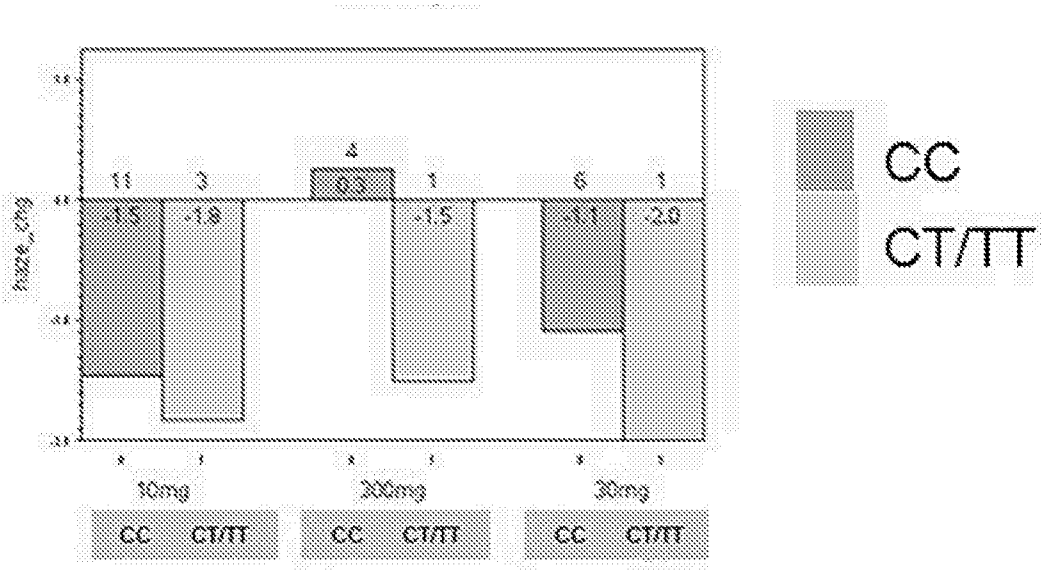

10mg
30mg
30mg
CC
CT/TT

Fig. 12

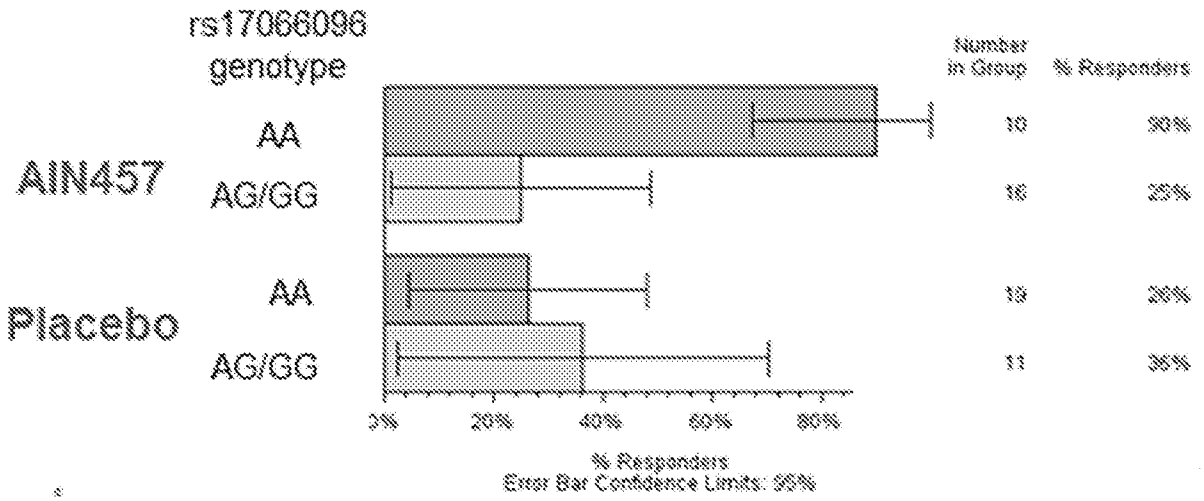

rs17066096
genotype
Number
in Group
% Responders
AIN457
AA
AG/GG
Placebo
AA
AG/GG
10
30%
16
25%
19
26%
11
35%
0%
20%
40%
60%
80%
% Responders
Error Bar Confidence Limits: 95%

Fig. 13

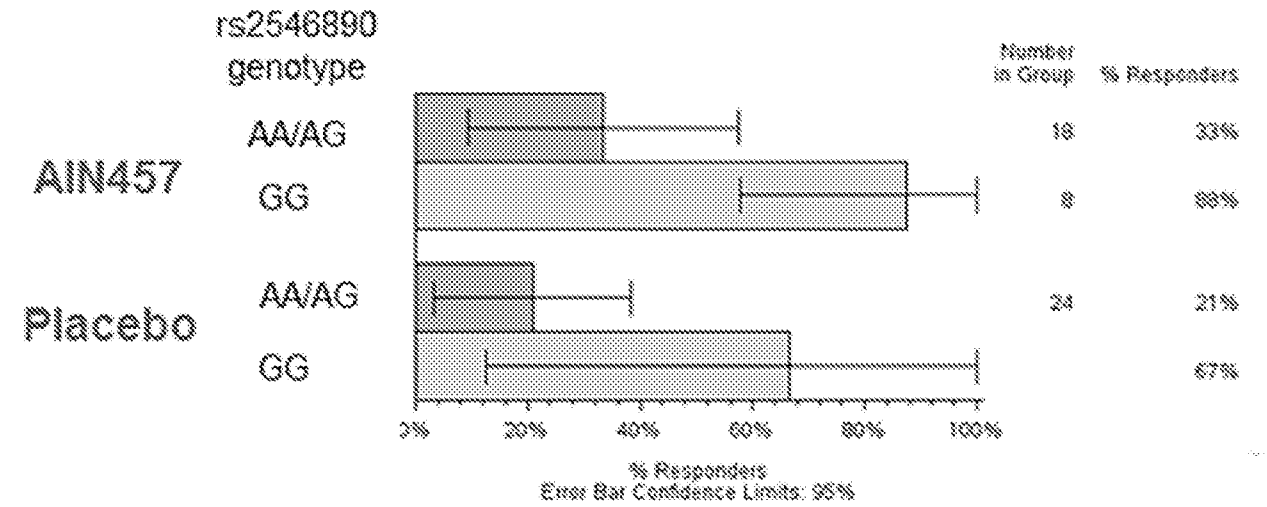

rs2546890
genotype
Number
in Group
% Responders
AIN457
AA/AG
GG
Placebo
AA/AG
GG
18
33%
9
89%
24
21%
67%
0%
20%
40%
60%
80%
100%
% Responders
Error Bar Confidence Limits: 95%

Fig. 14

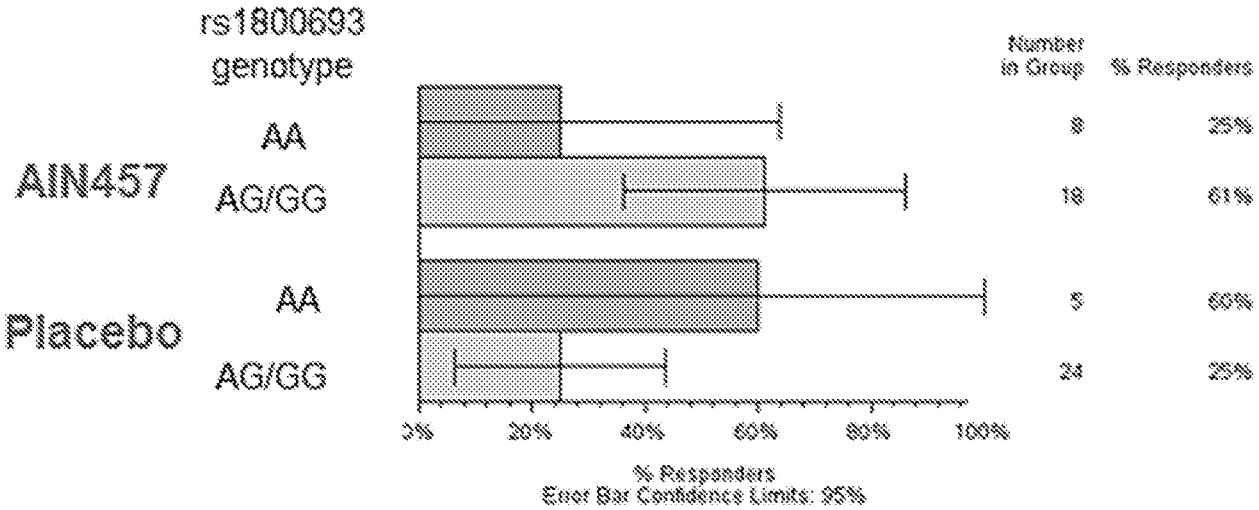

rs1800693
genotype
Number
in Group
% Responders
AIN457
AA
8
25%
AG/GG
18
61%
Placebo
AA
5
60%
AG/GG
24
25%
0%
20%
40%
60%
80%
100%
% Responders
Error Bar Confidence Limits: 95%

Fig. 15

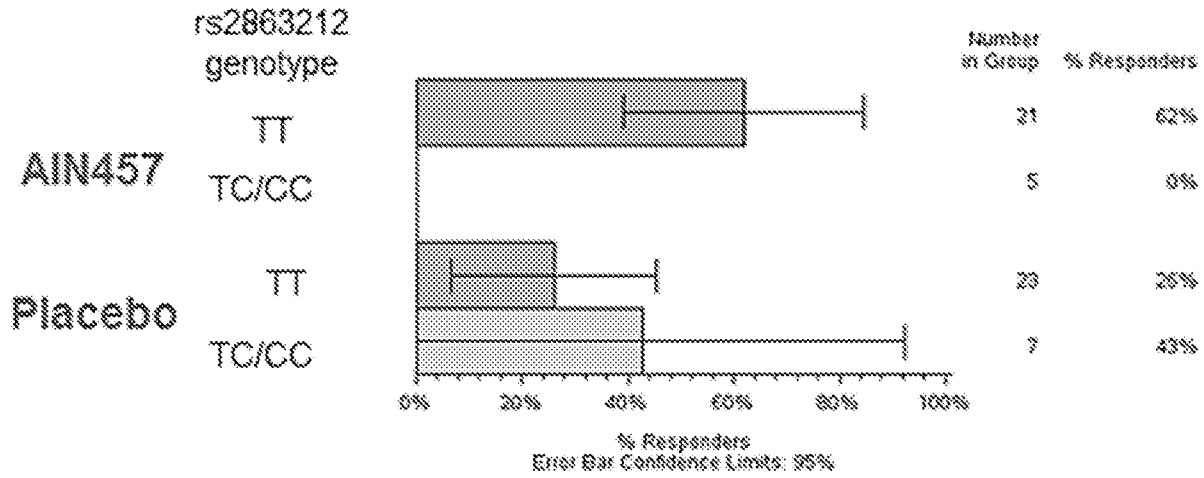

rs2863212
genotype
Number
in Group
% Responders
AIN457
TT
21
62%
TC/CC
5
0%
Placebo
TT
20
25%
TC/CC
7
43%
0%
20%
40%
60%
80%
100%
% Responders
Error Bar Confidence Limits: 95%

Fig. 16

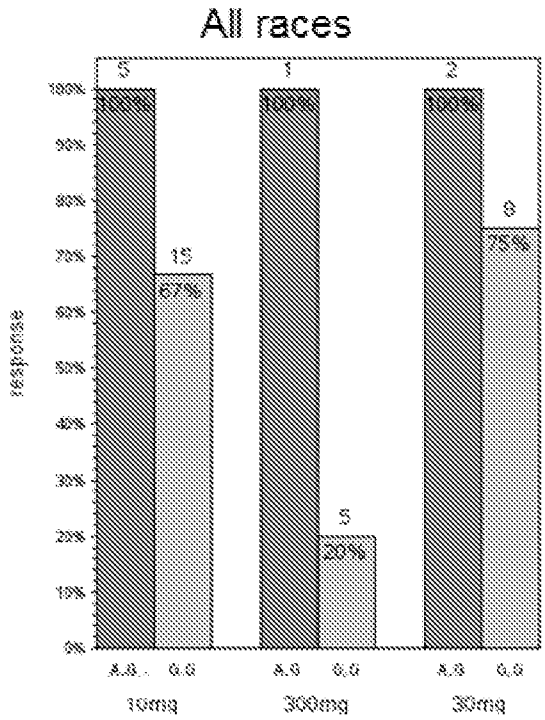

All races
response
5
100%
15
67%
1
100%
5
20%
2
100%
8
75%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
10mg
300mg
30mg

Fig. 17

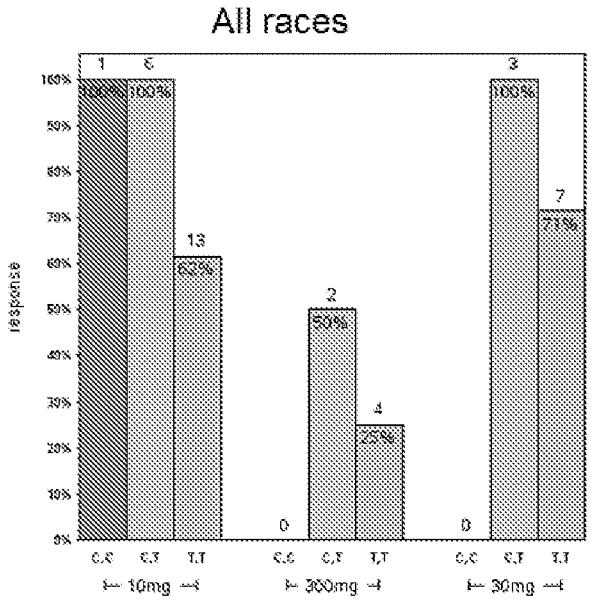

All races
Response
1
6
3
100%
100%
100%
13
62%
7
71%
2
50%
4
25%
0
0
C,C
C,T
T,T
10mg
300mg
30mg

Fig. 18

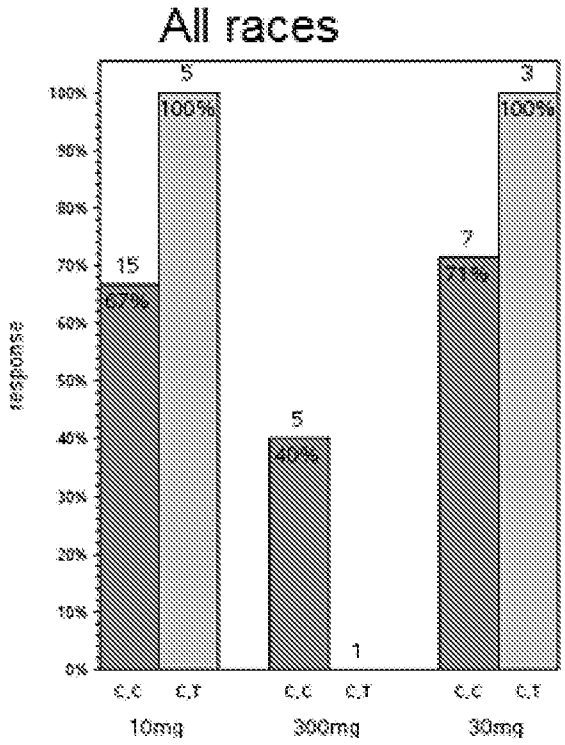
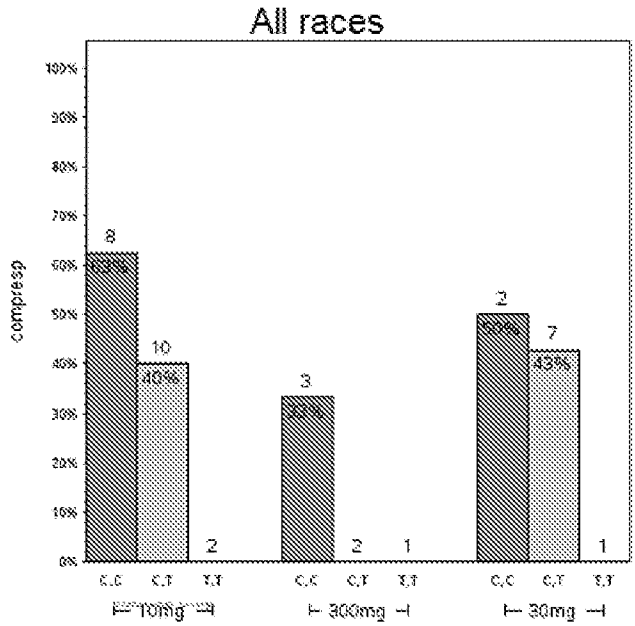

All races
response
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
15
67%
5
100%
5
40%
1
7
71%
3
100%
C,C
C,T
C,C
C,T
C,C
C,T
10mg
300mg
30mg

Fig. 19


All races
compresp
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
8
10
40%
2
3
2
1
2
7
43%
1
C,C
C,T
T,T
10mg
300mg
30mg