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(71) Applicant: NOVARTIS AG [CH/CH]; Lichtstrasse 35, 4056 Basel (CH).

(72) Inventor: GELFAND, Joel; The Trustees of the University of Pennsylvania, 3160 Chestnut Street, Suite 200, Philadelphia, PA 19104 (US).

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(54) Title: METHODS OF TREATING VITILIGO USING INTERLEUKIN-17 (IL-17) ANTIBODIES

(57) Abstract: The present disclosure relates to methods for treating vitiligo using IL-17 antagonists, e.g., secukinumab. Also disclosed herein are uses of IL-17 antagonists, e.g., IL-17 antibodies, such as secukinumab, for treating vitiligo patients, as well as medicaments, dosing regimens, pharmaceutical formulations, dosage forms, and kits for use in the disclosed uses and methods.



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METHODS OF TREATING VITILIGO USING INTERLEUKIN-17 (IL-17) ANTIBODIES

RELATED APPLICATIONS

The instant application claims priority to US Provisional Patent application No. 62/348217, filed June 10, 2016, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

The present disclosure relates to methods for treating vitiligo, using IL-17 antagonists, e.g., an IL-17 antibody or antigen-binding fragment thereof, such as secukinumab.

BACKGROUND OF THE DISCLOSURE

Vitiligo is a relatively common dermatological disorder, affecting about 1% of the population. (Kotobuki et al. (2012) *Pigment Cell Melanoma Res.* 25; 219–230). It is progressive, characterized by destruction of melanocytes within the epidermis, hair follicles, and possibly other organs, resulting in skin de-pigmentation. Vitiligo is officially categorized by location, i.e., segmental (occurring on one side of the body, typically as a single patch), non-segmental (occurring bilaterally), mixed, and unclassified. Non-segmental vitiligo tends to occur at sites sensitive to pressure or friction, and accounts for up to 90% of overall cases.

Despite extensive efforts over the years, vitiligo treatments are typically unsatisfactory to patients. Various creams and ointments prescribed for vitiligo patients can cause pimples, ingrown hairs, burning, itching and allergic reactions. Steroids and immunosuppressants can cause thinning of the skin, blood vessel formation, steroid-induced acne, atrophy, etc. Phototherapy can cause sunburn, redness, blistering, and inflammation. Moreover, vitiligo can be cosmetically very disabling to patients, particularly in individuals with darker skin. Indeed, recent reports indicate that the chronic nature of vitiligo, length of treatment, and lack of effective therapy are demoralizing for patients, leading to poor self-image and increased incidence of depression. (Al-Harbi (2013) *Skinmed* 11(6):327-30). Hence, there is a long-felt need for safe, effective, and non-invasive treatments for vitiligo.

SUMMARY OF THE DISCLOSURE

The cause of melanocyte loss in vitiligo patients is not clear, although there are three hypotheses for the pathogenesis: biochemical, neural, and autoimmune. (Khan et al. (2012) *J. Am. Acad. Dermatol.* 510-11). Although a cellular immune response, driven by CD8⁺ cytotoxic T cells against melanocyte-specific proteins, has been shown to destroy functional melanocytes in autoimmune vitiligo, this does not fully explain the cause of vitiligo. (Kotobuki 2012). Indeed, recent studies demonstrate increased expression of inflammatory cytokines, e.g., IL-2, TNF- α , IFN- γ , in vitiligo skin, and several studies propose that local cytokines in the skin may influence, induce and/or maintain vitiligo. (Kotobuki 2012).

Various studies have shown a positive correlation between serum IL-17 levels and the extent of vitiligo depigmentation patch area, elevated IL-17 levels in lesional skin and serum of patients with vitiligo, increased IL-17 gene expression in neutrophils of vitiligo patients, and elevated IL-17A mRNA levels and the presence of IL-17A⁺ T cells in the leading edge of vitiligo biopsies (Khan et al. (2012); Basak et al. (2009) *J. Am. Acad. Dermatol.* 60:256-60; , Bassiouny and Shaker (2011) *Clin. Exp. Dermatol.* 36:292-97; Esmaeili et al. (2011) *Iran J. Allergy Asthma Immunol.* 10(2):81-9; Wang et al. (2011) *PLoS One* 6(4):e18907; for a review see Singh et al. (2016) *Autoimmunity Reviews* 397-404). More recently, Kotobuki et al. identified a significant number of Th17 cells infiltrating vitiligo skin, and demonstrated an inhibitory effect of Th17 cell-related proinflammatory cytokines on melanocyte activity. (Kotobuki (2012)). In contrast, Jandus et al (2008) *Arthritis Rheum* 58: 2307–2317 report an increased number of circulating Th17 cells in the peripheral blood of patients with seronegative spondylarthritides (PsA and AS), but not in patients with RA or vitiligo. Thus, these mechanistic studies do not elucidate whether IL-17A is a driver of vitiligo disease, or merely a passenger of other mechanisms. In fact, in 2014 Bossard et al. reported induction of non-segmental vitiligo in a patient undergoing treatment with the IL-17 antagonist, secukinumab, suggesting that antagonism of IL-17 can, at least in some instances, induce melanocyte destruction. (Bossard et al. (2014) *Ann Rheum Dis* 73(Suppl2): 237; Mery-Bossard et al. (2017) *J Eur Acad Dermatol Venereol.* 31(1):181-186).

We have now determined that IL-17 antagonists, e.g., IL-17 antibodies, e.g., secukinumab, can be used systemically to treat vitiligo and resolve the skin de-pigmentation associated therewith.

Accordingly, disclosed herein are methods of treating vitiligo, comprising administering an IL-17 antagonist (e.g., an anti-IL-17 antibody or antigen-binding fragment thereof) to a patient in need thereof.

It is also contemplated that the disclosed methods, uses, kits and will find use in treating other skin hypopigmentation disorders characterized by Th17 or IL-17-induced destruction of melanocytes.

In some embodiments of the disclosed uses, methods and kits, the IL-17 antagonist is an IL-17 antibody or antigen-binding fragment thereof. In some embodiments of the disclosed uses, methods and kits, the IL-17 antibody or antigen-binding fragment thereof is selected from the group consisting of: a) an IL-17 antibody or antigen-binding fragment thereof 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 or antigen-binding fragment thereof that binds to an epitope of IL-17 comprising Tyr43, Tyr44, Arg46, Ala79, Asp80; c) an IL-17 antibody or antigen-binding fragment thereof 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 or antigen-binding fragment thereof 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 or antigen-binding fragment thereof has a K_D for human IL-17 of about 100-200 pM (e.g., about 200 pM), and wherein the IL-17 antibody or antigen-binding fragment thereof has an *in vivo* half-life of about 23 to about 35 days (e.g., about 27 days); and e) an IL-17 antibody or antigen-binding fragment thereof comprising: i) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8; ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10; iii) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence

set forth as SEQ ID NO:10; iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; v) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13; vii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; 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; ix) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14; x) an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15; or xi) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14 and an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15.

In some embodiments of the disclosed uses, methods and kits, the IL-17 antibody or antigen-binding fragment thereof is selected from the group consisting of: a) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of IL-17 between residues Arg 55 and Trp 67; b) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of IL-17 comprising Arg 55, Glu 57, and Trp 67; c) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of IL-17 comprising: Arg 55, Glu 57, Trp 67, Tyr 62, and Arg 101; d) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of IL-17 comprising Arg 55, Glu 57, Trp 67, Tyr 62, Arg 101, Pro 59, Ser 64, and Val 65; e) an IL-17 antibody or antigen-binding fragment thereof that binds to an epitope of IL-17 comprising Arg 55, Glu 57, Trp 67, Tyr 62, Arg 101, Pro 59, Ser 64, Val 65, Val 22*, Leu 26, Asp 58, Glu 60, Pro 63, Pro 107, Phe 110, and Lys 114*, where amino acids marked with (*) designate a residue contributed by the second IL-17 subunit of the IL-17A homodimer, wherein the IL-17 antibody or antigen-binding fragment thereof has a K_D for human IL-17 of about 1-10 pM (e.g., about 6 pM), and wherein the IL-17 antibody or antigen-binding fragment thereof has an *in vivo* half-life of about 14-23 days, e.g., about 20 days; and f) an IL-17 antibody or antigen-binding fragment thereof comprising: i) an immunoglobulin heavy chain variable domain (V_H) comprising the

amino acid sequence set forth as SEQ ID NO:30; ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:22; iii) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:30 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:22; iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:24, SEQ ID NO:26, and SEQ ID NO:28; v) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:16, SEQ ID NO:18 and SEQ ID NO:20; vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:25, SEQ ID NO:27 and SEQ ID NO:29; vii) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:17, SEQ ID NO:19 and SEQ ID NO:21; viii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:24, SEQ ID NO:26, and SEQ ID NO:28 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:16, SEQ ID NO:18 and SEQ ID NO:20; ix) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:25, SEQ ID NO:27, and SEQ ID NO:29 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:17, SEQ ID NO:19 and SEQ ID NO:21; x) a light chain comprising SEQ ID NO:23; xi) a heavy chain comprising SEQ ID NO:31; or xii) a light chain comprising SEQ ID NO:23 and a heavy chain comprising SEQ ID NO:31.

In some embodiments of the disclosed uses, methods and kits, the IL-17 antibody or antigen-binding fragment thereof is secukinumab (AIN457). Secukinumab is a high-affinity recombinant, fully human monoclonal anti-human interleukin-17A antibodies of the IgG1/ κ -class. Secukinumab binds to human IL-17A and neutralize the bioactivity of this cytokine.

DETAILED DESCRIPTION OF THE DISCLOSURE

As used herein, “vitiligo” refers to all forms of vitiligo, e.g., generalized (vitiligo vulgaris); acral, acrofacial and localized vitiligo (frequently referred to collectively as focal vitiligo); universal; segmental; non-segmental; unspecified; mixed; koebnerised; trichome; poliosis; and mucosal, unless otherwise stated. Vitiligo patients may have: 1) moderate to extensive vitiligo (body surface area (BSA) involvement $\geq 3\%$); 2) active vitiligo (- clear evidence of progression using digital pictures for follow-up (maximum time between the two observations = 7 months) and/or - disease progression during the last six months (as reported by the patient) or at least one

clinical activity sign (hypopigmented areas, vitiligo lesions with blurred borders or confetti-like depigmentations)); 3) vitiligo on hands and/or face; 4) fitzpatrick skin type 3-6; and/or 5) disease impact score $> 8/10$ or DLQI (Dermatology Life Quality Index) > 10). In some embodiments, the patient has moderate to extensive vitiligo. In some embodiments, the patient has active vitiligo. In some embodiments, the patient has moderate to extensive active vitiligo. In some embodiments, the patient has $\geq 3\%$ BSA involvement. In some embodiments, the patient has $\geq 15\%$ BSA involvement. In some embodiments, the patient has moderate to severe vitiligo by the Physicians Global Assessment Scoring system, based on it being chronic, affecting multiple sites and having $> 15\%$ BSA involvement.

As used herein, IL-17 refers to interleukin-17A (IL-17A).

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.

As used herein, the phrase “TNF-alpha antagonist” refers to small molecules and biological molecules capable of inhibiting, reducing and/or blocking TNF-alpha signal, transduction, and/or activity. Examples of TNF-alpha antagonists include Enbrel® (etanercept), Humira® (adalimumab), Remicade® (infliximab) and Simponi® (golimumab).

The term “about” in relation to a numerical value x means, for example, $\pm 10\%$. When used in front of a numerical range or list of numbers, the term “about” applies to each number in the series, e.g., the phrase “about 1-5” should be interpreted as “about 1 – about 5”, or, e.g., the phrase “about 1, 2, 3, 4” should be interpreted as “about 1, about 2, about 3, about 4, etc.”

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

The term "antibody" as referred to herein includes naturally-occurring and whole antibodies. A naturally-occurring "antibody" is a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region is comprised of one domain,

CL. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed 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. Exemplary antibodies include secukinumab (**Table 1**) and ixekizumab (U.S. Patent No. 7,838,638).

The term "antigen-binding fragment" 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 1**), 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.

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 processes and compositions, the IL-17 antibody is a human antibody, an isolated antibody, and/or a monoclonal antibody.

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

The term " K_D " is intended to refer to the dissociation rate of a particular antibody-antigen interaction. The term " K_D ", as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of K_d to K_a (i.e., K_d/K_a) and is expressed as a molar concentration (M). K_D values for antibodies can be determined using methods well established in the art. A method for determining the K_D of an antibody is by using surface plasmon resonance, or using a biosensor system such as a Biacore® system. In some embodiments, the IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab, binds human IL-17 with a K_D of about 1-250 pM, preferably about 100-200 pM (e.g., about 200 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 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 antibody or antigen-binding fragment thereof (e.g., secukinumab) to decrease IL-6 production from primary human dermal fibroblasts. The production of IL-6 in primary human (dermal) fibroblasts is dependent on IL-17 (Hwang et al., (2004) *Arthritis Res Ther*; 6:R120-128). In short, human dermal fibroblasts are stimulated with recombinant IL-17 in the presence of various concentrations of an IL-17 binding molecule or human IL-17 receptor with Fc part. The chimeric anti-CD25 antibody Simulect® (basiliximab) may be conveniently used as a negative control. Supernatant is taken after 16 h stimulation and assayed for IL-6 by ELISA. An IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab, typically has an IC₅₀ for inhibition of IL-6 production (in the presence 1 nM human IL-17) of about 50 nM or less (e.g., from about 0.01 to about 50 nM) when tested as above, i.e., said inhibitory activity being measured on IL-6 production induced by hu-IL-17 in human dermal fibroblasts. In some embodiments of the disclosed methods and compositions, IL-17 antibodies or antigen-binding fragments thereof, e.g., secukinumab, and functional derivatives thereof have an IC₅₀ for inhibition of IL-6 production as defined above of about 20 nM or less, more preferably of about 10 nM or less, more preferably of about 5 nM or less, more preferably of about 2 nM or less, more preferably of about 1 nM or less.

The term "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 antibody or antigen-binding fragment thereof, e.g., secukinumab, 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 antibodies. A functional derivative includes

fragments and peptide analogs of an IL-17 antibody 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 antibodies 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 antibodies and antigen-binding fragments thereof disclosed herein, 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 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 application. 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 an antibody 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 fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof) that is effective, upon single or multiple dose administration to a patient (such as a human) 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" is herein defined as the application or administration of

an IL-17 antibody according to the disclosure, for example, secukinumab or ixekizumab, or a pharmaceutical composition comprising said anti-IL-17 antibody, to a subject or to an isolated tissue or cell line from a subject, where the subject has a particular disease (e.g., vitiligo), a symptom associated with the disease (e.g., vitiligo), or a predisposition towards development of the disease (e.g., vitiligo), where the purpose is to cure (if applicable), delay the onset of, reduce the severity of, alleviate, ameliorate one or more symptoms of the disease, improve the disease, reduce or improve any associated symptoms of the disease or the predisposition toward the development of the disease. The term “treatment” or “treat” includes treating a patient suspected to have the disease as well as patients who are ill or who have been diagnosed as suffering from the disease or medical condition, and includes suppression of clinical relapse.

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. 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 criterion. 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 criterion. By selecting, selectively treating and selectively administering, it is meant that a patient is delivered a personalized therapy based on the patient’s personal history (e.g., prior therapeutic interventions, e.g., prior treatment with biologics), biology (e.g., particular genetic markers), and/or manifestation (e.g., not fulfilling particular diagnostic criteria), rather than being delivered a standard treatment regimen based solely on the patient’s membership in a larger group. Selecting, in reference to a method of treatment as used herein, does not refer to fortuitous treatment of a patient having a particular criterion, but rather refers to the deliberate choice to administer treatment to a patient based on the patient having a particular criterion. Thus, selective treatment/administration differs from standard treatment/administration, which delivers a particular drug to all patients having a particular disease, regardless of their personal history, manifestations of disease, and/or biology.

IL-17 Antagonists

The various disclosed processes, kits, uses and methods utilize an IL-17 antagonist. IL-17 antagonists include small molecules and biological molecules that are capable of blocking, reducing and/or inhibiting IL-17 signal, activity and/or transduction. Examples of IL-17 antagonists include e.g., IL-17 binding molecules (e.g., soluble IL-17 receptors, IL-17 antibodies or antigen-binding fragments thereof, e.g., secukinumab) and IL-17 receptor binding molecules (e.g., IL-17 receptor antibodies or antigen-binding fragments thereof). In some embodiments, the IL-17 antagonist is an IL-17 binding molecule, preferably an IL-17 antibody or antigen-binding fragment thereof. IL-17 antibodies and antigen-binding fragment thereof as used herein can be fully-human, CDR-grafted, or chimeric. It is preferable that the constant region domains of an antibody or antigen-binding fragment thereof for use in the disclosed methods, uses, kits, etc. preferably 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.

Particularly preferred IL-17 antibodies or antigen-binding fragments thereof used in the disclosed methods are human antibodies, especially secukinumab as described in Examples 1 and 2 of WO 2006/013107, which is incorporated by reference herein in its entirety. Secukinumab is a recombinant high-affinity, fully human monoclonal anti-human interleukin-17A (IL-17A, IL-17) antibody of the IgG₁/kappa isotype. Secukinumab has a high affinity for IL-17, i.e., a K_D of about 100-200 pM (e.g., about 200 pM), an IC₅₀ for *in vitro* neutralization of the biological activity of about 0.67 nM human IL-17A of about 0.4 nM, and a half-life of about 4 weeks.

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 1**, below.

Light-Chain		
CDR1'	Kabat	R-A-S-Q-S-V-S-S-S-Y-L-A (SEQ ID NO:4)
	Chothia	R-A-S-Q-S-V-S-S-S-Y-L-A (SEQ ID NO:4)

CDR2'	Kabat	G-A-S-S-R-A-T (SEQ ID NO:5)
	Chothia	G-A-S-S-R-A-T (SEQ ID NO:5)
CDR2'	Kabat	Q-Q-Y-G-S-S-P-C-T (SEQ ID NO:6)
	Chothia	Q-Q-Y-G-S-S-P-C-T (SEQ ID NO:6)
Heavy-Chain		
CDR1	Kabat	N-Y-W-M-N (SEQ ID NO:1)
CDR1-x	Chothia	G-F-T-F-S-N-Y-W-M-N (SEQ ID NO:11)
CDR2	Kabat	A-I-N-Q-D-G-S-E-K-Y-Y-V-G-S-V-K-G (SEQ ID NO:2)
CDR2-x	Chothia	A-I-N-Q-D-G-S-E-K-Y-Y (SEQ ID NO:12)
CDR3	Kabat	D-Y-Y-D-I-L-T-D-Y-Y-I-H-Y-W-Y-F-D-L (SEQ ID NO:3)
CDR3-x	Chothia	C-V-R-D-Y-Y-D-I-L-T-D-Y-Y-I-H-Y-W-Y-F-D-L-W-G (SEQ ID NO:13)

Table 1: Amino acid sequences of the hypervariable regions of secukinumab. 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 one embodiment, the IL-17 antibody or antigen-binding fragment thereof 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 antibody or antigen-binding fragment thereof 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 antibody or antigen-binding fragment thereof 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 antibody or antigen-binding fragment thereof 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 antibody or antigen-binding fragment thereof comprises: a) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8; b) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10; c) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10; d) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; e) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; f) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13; g) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; or h) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11,

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

In some embodiments, the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab) comprises the three CDRs of SEQ ID NO:10. In other embodiments, the IL-17 antibody or antigen-binding fragment thereof comprises the three CDRs of SEQ ID NO:8. In other embodiments, the IL-17 antibody or antigen-binding fragment thereof 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 may be found in **Table 1**. The free cysteine in the light chain (CysL97) may be seen in SEQ ID NO:6.

In some embodiments, IL-17 antibody or antigen-binding fragment thereof comprises the light chain of SEQ ID NO:14. In other embodiments, the IL-17 antibody or antigen-binding fragment thereof comprises the heavy chain of SEQ ID NO:15. In other embodiments, the IL-17 antibody or antigen-binding fragment thereof comprises the light chain of SEQ ID NO:14 and the heavy domain of SEQ ID NO:15. In some embodiments, the IL-17 antibody or antigen-binding fragment thereof comprises the three CDRs of SEQ ID NO:14. In other embodiments, IL-17 antibody or antigen-binding fragment thereof comprises the three CDRs of SEQ ID NO:15. In other embodiments, the IL-17 antibody or antigen-binding fragment thereof comprises the three CDRs of SEQ ID NO:14 and the three CDRs of SEQ ID NO:15. CDRs of SEQ ID NO:14 and SEQ ID NO:15 may be found in **Table 1**.

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 antibody or antigen-binding fragment thereof (e.g., secukinumab) is selected from a human IL-17 antibody that 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 antibody or antigen-binding fragment thereof is selected from a single chain antibody or antigen-binding fragment thereof that 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, in sequence, 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 antibody or antigen-binding fragment thereof as used in the disclosed methods may comprise a derivative of the IL-17 antibodies set forth herein by sequence (e.g., a pegylated version of secukinumab). Alternatively, the V_H or V_L domain of an IL-17 antibody or antigen-binding fragment thereof used in the disclosed methods may have V_H or V_L domains that are substantially identical to the V_H or V_L domains 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:15 and/or a light chain that is substantially identical to that set forth as SEQ ID NO:14. A human IL-17 antibody disclosed herein may

comprise a heavy chain that comprises SEQ ID NO:15 and a light chain that comprises SEQ ID NO:14. A human IL-17 antibody disclosed herein may comprise: a) one heavy chain, comprising 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, comprising 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 antibody or antigen-binding fragment thereof used in the disclosed methods may be an amino acid sequence variant of the reference IL-17 antibodies set forth herein, as long as it contains CysL97. The disclosure also includes IL-17 antibodies or antigen-binding fragments thereof (e.g., secukinumab) in which one or more of the amino acid residues of the V_H or V_L domain of secukinumab (but not CysL97), typically only a few (e.g., 1-10), are changed; for instance by mutation, e.g., site directed mutagenesis of the corresponding DNA sequences. In all such cases of derivative and variants, the IL-17 antibody or antigen-binding fragment thereof 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 as described in Example 1 of WO 2006/013107.

In some embodiments, the IL-17 antibodies or antigen-binding fragments thereof, e.g., secukinumab, bind 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 (i.e., 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 (SC) administered IL-17 antibody has a range of about 60 – about 80%, e.g., about 76%. In some embodiments, the IL-17 antibody, such as secukinumab, 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 antibody (such as secukinumab) has a T_{max} of about 7-8 days.

Other preferred IL-17 antagonists (e.g., antibodies) for use in the disclosed methods, kits and regimens include KHK4872 (Kyowa Hakko Kirin), ABT-122 (Abbvie), BCD-085 (JCS Biopharm), vidofludimus (4SC-101), NI-1401 (RG7624; MCAF5352A - NovImmune), ANB004 (AnaptysBio Inc.), E-036041 (Ensemble Therapeutics Corp.), Q β -IL-17 (virus-like particle-based vaccine), PRS-190 (Pieris AG) bimekizumab (UCB 4940 – UCB), ALX-0761, CNTO 6785 (Janssen Pharmaceuticals), LY3074828 (Eli Lilly), LY3114062 (Eli Lilly), SCH-900117, MSB0010841 (ALX-0761 – Merck), ABT-122, COVA322 (Covagen), ixekizumab and brodalumab, as well as those set forth in US Patent Nos: 9,193,788; 8,057,794; 7,767,206; 8,003,099; 8,110,191; and 7,838,638 and US Published Patent Application Nos: 20120034656 and 20110027290, which are incorporated by reference herein in their entirety.

Methods of Treatment and Uses of IL-17 Antagonists for Vitiligo

The disclosed IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 receptor antibody or antigen-binding fragment thereof), may be used *in vitro*, *ex vivo*, or incorporated into pharmaceutical compositions and administered *in vivo* to treat vitiligo (e.g., human patients having vitiligo). Response of patients to treatment may be measured using various well-known vitiligo scoring means, e.g., the Vitiligo Area Scoring Index (VASI), the Vitiligo European Task Force (VETF) system, Vitiligo Extent Tensity Index (VETI) (Feily (2014) Dermatol Pract Concept 4(4)81-4), Vitiligo Disease Activity Score (VIDA), Potential Repigmentation Index (PRI) (Benzekri et al (2013) Br J Dermatol. 168:1143–6), percentage repigmentation as measured using the physician's global assessment (PGA), the Vitiligo Quality of Life (VitiQOL) tool, Dermatology Life Quality Index (DLQI), Global Impact Score, or Global Satisfaction Score, e.g., the Likert scale, the improvement assessment scale proposed by Hossain (Hossain (2005) J Am Acad Dermatol 52(6) 110-111). It is contemplated that all responsive

forms of vitiligo may be treated using the disclosed uses, compositions, methods and kits, e.g., generalized (vitiligo vulgaris); acral, acrofacial and localized vitiligo (frequently referred to collectively as focal vitiligo); universal; segmental; non-segmental; unspecified; mixed; koebnerised; trichome; poliosis; and mucosal. In some embodiments, the patient experiences at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or 100% repigmentation following 8, 12, 16, 20, 24, 36, 48, 52 or 104 weeks of treatment according to the claimed methods.

The IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof), may be used as a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may contain, in addition to an IL-17 antagonist, carriers, various diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The characteristics of the carrier will depend on the route of administration. The pharmaceutical compositions for use in the disclosed methods may also contain additional therapeutic agents for treatment of the particular targeted disorder. For example, a pharmaceutical composition may also include anti-inflammatory agents. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with the IL-17 binding molecules, or to minimize side effects caused by the IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof).

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 fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof) is administered by intravenous, cutaneous or subcutaneous injection, the IL-17 antagonist will be in the form of a pyrogen-free, parenterally acceptable solution. A pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection may contain, in addition to the IL-17 antagonist, an isotonic vehicle such as sodium chloride, Ringer's solution, dextrose, dextrose and sodium chloride, lactated Ringer's solution, or other vehicle as known in the art.

The appropriate dosage will vary depending upon, for example, on the particular IL-17 antagonists employed, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof), 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 fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof) is administered to a patient, e.g., a mammal (e.g., a human). While it is understood that the disclosed methods provide for treatment of vitiligo patients using an IL-17 antagonist (e.g., secukinumab), this does not preclude that, if the patient is to be 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 methods of the disclosure either alone or in combination with other agents and therapies (e.g., phototherapy, such as whole-body or localized broadband or narrow band UVB; excimer laser UVB; targeted UVB; and/or oral, topical or bathwater photochemotherapy (PUVA) for treating vitiligo patients, e.g., in combination with at least one additional vitiligo agent, such as a topical or systemic steroid, e.g., a corticosteroid cream; an immunosuppressive agent (e.g., a calcineurin inhibitor, e.g., pimecrolimus and tacrolimus (e.g., ointments or creams, e.g., ELIDEL™)); an antibiotic (e.g., tetracycline antibiotics, e.g., oral minocycline); afamelanotide; pseudocatalase cream; novitil; V-Tar; sinvitil; calcipotriene; psoralen; retinoids, oral acitretin, a cytokine modulator (e.g., an agonist or antagonist of IL-2, TNF- α , TGF- β , IL-4, IFN- γ , IL-6, IL-23 (e.g., ustekinumab), etc.), and combinations thereof (e.g., dual and triple therapies); triamcinolone; abatacept; rilonacept; simvastatin; bimatoprost; atorvastatin; and a TNF alpha antagonist (e.g., adalimumab, etanercept, remicade, etc.). Steroids (e.g., glucocorticoids) useful in combination with an IL-17 antagonist, e.g., secukinumab, for the treatment of a vitiligo patient include, but are not limited to, prednisolone, prednisone, dexamethasone, fluocinolone acetonide, mometasone, cortisol, cortisone, hydrocortisone, methylprednisolone, betamethasone, triamcinolone, beclometasone, fludrocortisone, deoxycorticosterone, aldosterone. When coadministered with one or more additional vitiligo agents, an IL-17 antagonist may be administered either simultaneously with the other agent, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering the IL-17 antagonist in combination with other agents and the appropriate dosages for co-delivery. An IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-

IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding fragment thereof) is conveniently administered parenterally, e.g., intravenously (e.g., into the antecubital or other peripheral vein), intramuscularly, or subcutaneously. The duration of intravenous (IV) 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 (SC) therapy using a pharmaceutical composition of the present disclosure. The health care provider will decide on the appropriate duration of IV or SC therapy and the timing of administration of the therapy, using the pharmaceutical composition of the present disclosure.

Preferred treatment regimens (including both induction and maintenance regimens) using secukinumab, which may be employed in treating vitiligo patients, are provided in PCT Application No. PCT/US2011/064307 and PCT/IB2014/063902, which are incorporated by reference herein in their entirety.

The IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding fragment thereof) may be administered to the vitiligo patient intravenously (IV) at about 10 mg/kg every other week during week 0, 2, and 4 and thereafter administered to the patient subcutaneously (SC) at about 75 mg – about 300 mg (e.g., about 75 mg, about 150 mg, about 300 mg) monthly, beginning during week 8. In this manner, the patient is dosed IV with about 10 mg/kg during week 0, 2, 4, and then the patient is dosed SC with about 75 mg – about 300 mg (e.g., about 75 mg, about 150 mg, about 300 mg) of the IL-17 antagonist (e.g., secukinumab) during week 8, 12, 16, 20, etc.

The IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding fragment thereof) may be administered to the patient SC at about 75 mg – about 300 mg (e.g., about 75 mg, about 150 mg, about 300 mg) weekly during weeks 0, 1, 2, and 3, and thereafter administered to the patient SC at about 75 mg – about 300 mg (e.g., about 75 mg, about 150 mg, about 300 mg) monthly, beginning during week 4. In this manner, the patient is dosed SC with about 75 mg – about 300 mg (e.g., about 75 mg, about 150

mg, about 300 mg) of the IL-17 antagonist (e.g., secukinumab) during weeks 0, 1, 2, 3, 4, 8, 12, 16, 20, etc.

Alternatively, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding fragment thereof) may be administered to the patient without a loading regimen, e.g., the antagonist may be administered to the patient SC at about 75 mg – about 300 mg (e.g., about 75 mg, about 150 mg, about 300 mg) every 4 weeks (monthly). In this manner, the patient is dosed SC with about 75 mg – about 300 mg (e.g., about 75 mg, about 150 mg, about 300 mg) of the IL-17 antagonist (e.g., secukinumab) during weeks 0, 4, 8, 12, 16, 20, etc. In some cases, dosing may be weekly, bimonthly (every 2 weeks), monthly (every 4 weeks), every other month, quarterly (every three months), biyearly (every 6 months), or yearly.

Preferred S.C. doses are 150 mg - 300 mg, preferably 150 mg or 300 mg. However, it will be understood that dose escalation may be required (e.g., during an induction and/or maintenance phase) for certain patients, e.g., patients that display inadequate response to treatment with the IL-17 antagonists, e.g., IL-17 binding molecules (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecules (e.g., IL-17 receptor antibody or antigen-binding fragment thereof). Thus, SC dosages of secukinumab may be greater than about 150 mg to about 300 mg SC, e.g., about 175 mg, about 200 mg, about 250 mg, about 350 mg, about 400 mg, about 600 mg, etc.; similarly, IV 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., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab). Thus, dosages of the IL-17 antagonist (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab), may be less than about 150 mg to about 300 mg SC, e.g., about 25 mg, about 50 mg, about 80 mg, about 100 mg, about 125 mg, about 175 mg, about 200 mg, about 250 mg, about 275 mg, etc.; similarly, IV 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. In some embodiments, the IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17

receptor binding molecule (e.g., IL-17 receptor antibody or antigen-binding fragment thereof) may be administered to the patient at an initial dose (or doses) of 150 mg delivered SC, and the dose is then escalated to about 300 mg if needed, as determined by a physician.

The timing of dosing is generally measured from the day of the first dose of secukinumab (which is also known as “baseline”). However, health care providers often use different naming conventions to identify dosing schedules, as shown in **Table 2**.

Week	0/1	1/2	2/3	3/4	4/5	5/6	6/7	7/8	8/9	9/10	10/11	etc
1 st day of week	0/1	7/8	14/15	21/22	28/29	35/36	42/43	49/50	56/57	63/64	70/71	etc.

Table 2: Common naming conventions for dosing regimens. Bolded items refer to the naming convention used herein.

Notably, week zero may be referred to as week one by some health care providers, while day zero may be referred to as day one by some health care providers. Thus, it is possible that different physicians will designate, e.g., a dose as being given during week 3 / on ~ day 21, during week 3 / on ~ day 22, during week 4 / on ~ day 21, during week 4 / on ~ day 22, while referring to the same dosing schedule. For consistency, the first week of dosing will be referred to herein as week 0, while the first day of dosing will be referred to as day 1. However, it will be understood by a skilled artisan that this naming convention is simply used for consistency and should not be construed as limiting, i.e., weekly dosing is the provision of a weekly dose of the IL-17 antibody regardless of whether the physician refers to a particular week as “week 1” or “week 2”. In one dosing regimen, the antibody is administered monthly during week 0, 4, 8, 12, 16, etc. In one dosing regimen, the antibody is administered during week 0, 1, 2, 3, 4, 8, 12, 16, 20, etc. Some providers may refer to this regimen as weekly for five weeks and then monthly (or every 4 weeks) thereafter, beginning during week 8, while others may refer to this regimen as weekly for four weeks and then monthly (or every 4 weeks) thereafter, beginning during week 4. Thus, it will be appreciated by a skilled artisan that administering a patient an injection at weeks 0, 1, 2 and 3, followed by once monthly dosing starting at week 4 is the same as: 1)

administering the patient an injection at weeks 0, 1, 2, 3, and 4, followed by once monthly dosing starting at week 8; 2) administering the patient an injection at weeks 0, 1, 2, 3 and 4 followed by dosing every 4 weeks; and 3) administering the patient an injection at weeks 0, 1, 2, 3 and 4 followed by monthly administration.

Disclosed herein are methods of treating a patient having vitiligo, comprising administering an IL-17 antibody or antigen-binding fragment thereof to a patient in need thereof, wherein the IL-17 antibody or antigen-binding fragment thereof 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 or antigen-binding fragment thereof has a K_D for human IL-17 of about 100-200 pM, and wherein the IL-17 antibody or antigen-binding fragment thereof has an *in vivo* half-life of about 4 weeks.

Additionally disclosed herein are IL-17 antagonists (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) for use in treating a patient having vitiligo, wherein the IL-17 antagonist (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) 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 or antigen-binding fragment thereof has a K_D for human IL-17 of about 100-200 pM, and wherein the IL-17 antibody or antigen-binding fragment thereof has an *in vivo* half-life of about 4 weeks.

Additionally disclosed herein are IL-17 antagonists (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) for use in the manufacture of a medicament for treating a patient having vitiligo, wherein the IL-17 antagonist (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) 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 or antigen-binding fragment thereof has a K_D for human IL-17 of about 100-200 pM, and wherein the IL-17 antibody or antigen-binding fragment thereof has an *in vivo* half-life of about 4 weeks.

Additionally disclosed herein are IL-17 antagonists (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) for use in the manufacture of a medicament for treating a patient having vitiligo, wherein the medicament is formulated to comprise containers, each container having a sufficient amount of the IL-17 antagonist (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) to allow subcutaneous delivery of at least about 75 mg – about 300 mg (e.g., about 75 mg, about 150 mg, about 300 mg) of the IL-17 antagonist (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) per unit dose, and further wherein the IL-17 antagonist (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) 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 or antigen-binding fragment thereof has a K_D for human IL-17 of about 100-200 pM, and wherein the IL-17 antibody or antigen-binding fragment thereof has an *in vivo* half-life of about 4 weeks.

As used herein, the phrase “formulated at a dosage to allow [route of administration] delivery of [a designated dose]” is used to mean that a given pharmaceutical composition can be used to provide a desired dose of an IL-17 antagonist, e.g., an IL-17 antibody, e.g., secukinumab, via a designated route of administration (e.g., SC or IV). As an example, if a desired subcutaneous dose is 300 mg, then a clinician may use 2 ml of an IL-17 antibody formulation having a concentration of 150 mg/ml, 1 ml of an IL-17 antibody formulation having a concentration of 300 mg/ml, 0.5 ml of an IL-17 antibody formulation having a concentration of 600 mg/ml, etc. In each such case, these IL-17 antibody formulations are at a concentration high enough to allow subcutaneous delivery of the IL-17 antibody. Subcutaneous delivery typically requires delivery of volumes of less than about 2 ml, preferably a volume of about 1 ml or less. Preferred formulations are liquid pharmaceutical compositions comprising about 25 mg/mL to about 150 mg/mL secukinumab, about 10 mM to about 30 mM histidine pH 5.8, about 200 mM to about 225 mM trehalose, about 0.02% polysorbate 80, and about 2.5 mM to about 20 mM methionine.

As used herein, the phrase “container having a sufficient amount of the IL-17 antagonist to allow delivery of [a designated dose]” is used to mean that a given container (e.g., vial, pen, syringe) has disposed therein a volume of an IL-17 antagonist (e.g., as part of a pharmaceutical

composition) that can be used to provide a desired dose. As an example, if a desired dose is 150 mg, then a clinician may use 2 ml from a container that contains an IL-17 antibody formulation with a concentration of 75 mg/ml, 1 ml from a container that contains an IL-17 antibody formulation with a concentration of 150 mg/ml, 0.5 ml from a container contains an IL-17 antibody formulation with a concentration of 300 mg/ml, etc. In each such case, these containers have a sufficient amount of the IL-17 antagonist to allow delivery of the desired 150 mg dose.

In some embodiments of the disclosed uses, methods, and kits, the patient has a concomitant autoimmune disease, e.g., myasthenia gravis, thyoma, polymyositis and giant cell myocarditis, alopecia areata, scleroderma, inflammatory bowel disease (ulcerative colitis or Crohn's), ankylosing spondylitis, psoriatic arthritis, Sjögren's syndrome, rheumatoid arthritis (RA), primary biliary cirrhosis (PBC), scleroderma, autoimmune thyroid disease, multiple sclerosis, uveitis, type 1 diabetes mellitus, morphoea, discoid lupus erythematosus, pemphigus erythematosus, Grave's disease, systemic (or cutaneous) lupus, pernicious anemia, idiopathic thrombopenic purpura (ITP), Addison's disease, autoimmune hemolytic anemia (AIHA), dermatitis herpetiformis, or psoriasis (e.g., moderate to severe psoriasis), etc.

In some embodiments of the disclosed uses, methods, and kits, the patient is additionally administered a steroid, an antibiotic or a TNF-alpha antagonist.

In some embodiments of the disclosed uses, methods, and kits, the patient is administered about 75 mg – about 300 mg (e.g., about 150 mg – about 300 mg) of the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab) by subcutaneous injection at weeks 0, 1, 2 and 3, followed by once monthly dosing starting at week 4. In some embodiments of the disclosed uses, methods, and kits, the patient is administered 150 mg or 300 mg of the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab) by subcutaneous injection at weeks 0, 1, 2 and 3, followed by once monthly dosing starting at week 4.

In some embodiments of the disclosed uses, methods, and kits, the patient is monthly administered about 75 mg – about 300 mg (e.g., about 150 mg – about 300 mg) of the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab) by subcutaneous injection. In some embodiments of the disclosed uses, methods, and kits, the patient is monthly administered 150 mg or 300 mg of the IL-17 antibody or antigen-binding fragment thereof (e.g., secukinumab) by subcutaneous injection.

In some embodiments of the disclosed uses, methods, and kits, the IL-17 antibody or

antigen-binding fragment thereof comprises: i) an immunoglobulin heavy chain variable domain (V_H) comprising the amino acid sequence set forth as SEQ ID NO:8; ii) an immunoglobulin light chain variable domain (V_L) comprising the amino acid sequence set forth as SEQ ID NO:10; iii) an immunoglobulin V_H domain comprising the amino acid sequence set forth as SEQ ID NO:8 and an immunoglobulin V_L domain comprising the amino acid sequence set forth as SEQ ID NO:10; iv) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; v) an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; vi) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:11, SEQ ID NO:12 and SEQ ID NO:13; vii) an immunoglobulin V_H domain comprising the hypervariable regions set forth as SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 and an immunoglobulin V_L domain comprising the hypervariable regions set forth as SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6; 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; ix) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14; x) an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15; or xi) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14 and an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15. In some embodiments of the disclosed uses, methods, and kits, the IL-17 antibody or antigen-binding fragment thereof is secukinumab.

Disclosed herein are also methods of treating a patient having vitiligo, comprising administering the patient about 150 mg – about 300 mg of secukinumab by subcutaneous injection at weeks 0, 1, 2 and 3, followed by once monthly dosing starting at week 4. Disclosed herein are also methods of treating a patient having vitiligo, comprising monthly administering the patient about 150 mg – about 300 mg of secukinumab by subcutaneous injection. Disclosed herein are also methods of treating a patient having vitiligo, comprising monthly administering the patient about 150 mg of secukinumab by subcutaneous injection. Disclosed herein are also methods of treating a patient having vitiligo, comprising monthly administering the patient about 300 mg of secukinumab by subcutaneous injection.

Kits

The disclosure also encompasses kits for treating a vitiligo patient. Such kits comprise an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen-binding fragment thereof) (e.g., in liquid or lyophilized form) or a pharmaceutical composition comprising the IL-17 antagonist (described *supra*). Additionally, such kits may comprise means for administering the IL-17 antagonist (e.g., an autoinjector, 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 vitiligo, e.g., for delivery in combination with the enclosed IL-17 antagonist, e.g., IL-17 binding molecule, e.g., IL-17 antibody, e.g., secukinumab. Such kits may also comprise instructions for administration of the IL-17 antagonist (e.g., IL-17 antibody, e.g., secukinumab) to treat the vitiligo patient. Such instructions may provide the dose (e.g., 10 mg/kg, 75 mg, 150 mg, 300 mg), route of administration (e.g., IV, SC), and dosing regimen (e.g., about 10 mg/kg given IV, every other week during weeks 0, 2, and 4, and thereafter at about 75 mg, about 150 mg, or about 300 mg given SC monthly, beginning during week 8; about 75 mg, about 150 mg, or about 300 mg given SC weekly during week 0, 1, 2, and 3 and thereafter at about 75 mg, about 150 mg, or about 300 mg given SC monthly, beginning during week 4; about 75 mg, about 150 mg, or about 300 mg given SC monthly, etc.) for use with the enclosed IL-17 antagonist, e.g., IL-17 binding molecule, e.g., IL-17 antibody, e.g., secukinumab.

The phrase “means for administering” is used to indicate any available implement for systemically administering a drug to a patient, including, but not limited to, a pre-filled syringe, a vial and syringe, an injection pen, an autoinjector, an IV drip and bag, a pump, etc. With such items, a patient may self-administer the drug (i.e., administer the drug without the assistance of a physician) or a medical practitioner may administer the drug.

Disclosed herein are kits for use in treating a patient having vitiligo, comprising an IL-17 antagonist (e.g., IL-17 binding molecule, e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab). In some embodiments, the kit further comprises means for administering the IL-17 antagonist to the patient. In some embodiments, the kit further comprises instructions for administration of the IL-17 antagonist, wherein the instructions indicate that the IL-17 antagonist (e.g., IL-17 binding molecule, e.g., IL-17 antibody or antigen-binding fragment

thereof, e.g., secukinumab) is to be administered to the patient intravenously (IV) at about 10 mg/kg every other week during week 0, 2, and 4 and thereafter is to be administered to the patient subcutaneously (SC) at about 75 mg – about 300 mg (e.g., about 75 mg, about 150 mg, or about 300 mg) monthly, beginning during week 8. In some embodiments, the kit further comprises instructions for administration of the IL-17 antagonist, wherein the instructions indicate that the IL-17 antagonist (e.g., IL-17 binding molecule, e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) is to be administered to the patient SC with or without a loading regimen, e.g., at about 75 mg – about 300 mg (e.g., about 75 mg, about 150 mg, or about 300 mg): a) weekly during weeks 0, 1, 2, and 3, and thereafter SC at about 75 mg – about 300 mg (e.g., about 75 mg, about 150 mg, or about 300 mg) monthly, beginning during week 4; or b) every month (every 4 weeks). In some embodiments, the instructions will provide for dose escalation (e.g., from a dose of about 75 mg to a higher dose of about 150 mg or about 300 mg as needed, to be determined by a physician).

In some embodiments, the kit further comprises instructions for administration of the IL-17 antagonist, wherein the instructions indicate that the IL-17 antagonist (e.g., IL-17 binding molecule, e.g., IL-17 antibody or antigen-binding fragment thereof, e.g., secukinumab) is to be administered to the patient SC at about 75 mg – about 300 mg (e.g., about 75 mg, about 150 mg, or about 300 mg): a) weekly during weeks 0, 1, 2, and 3, and thereafter is to be administered to the patient SC at about 75 mg – about 300 mg (e.g., about 75 mg, about 150 mg, or about 300 mg) monthly, beginning during week 4; or b) every month (every 4 weeks). In some embodiments, the instructions will provide for dose escalation (e.g., from a dose of about 75 mg to a higher dose of about 150 mg or about 300 mg as needed, to be determined by a physician).

General

In preferred embodiments of the disclosed methods, treatments, medicaments, regimens, uses and kits, the IL-17 antagonist is an IL-17 binding molecule. In preferred embodiments, the IL-17 binding molecule is an IL-17 antibody or antigen-binding fragment thereof. In preferred embodiments of the disclosed methods, treatments, regimens, uses and kits, the IL-17 antibody or antigen-binding fragment thereof is a human antibody of the IgG₁ isotype. In preferred embodiments of the disclosed methods, the antibody or antigen-binding fragment thereof 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.

EXAMPLE

There are two main clinical variants of vitiligo: generalized (non-segmental) vitiligo, characterized by symmetrical patchy white areas that may spread to any part of the body; and segmental vitiligo, defined by unilateral depigmented macules. There are several subtypes of vitiligo applicable to both variants. Focal vitiligo is characterized by one or few small macules; periorificial vitiligo involves skin around the eyes, nose, ears, mouth, and anus; acrofacial vitiligo affects periorificial facial areas and distal extremities; mucosal vitiligo affects the oral and/or genital mucosa; and vitiligo universalis refers to generalized vitiligo with complete or almost complete depigmentation. Guidelines for vitiligo trial design and results reporting may be found in Gonzalez et al. (2011) Arch. Dermatol. 147(12):1428-36.

The objective of the study is to assess the efficacy and safety of secukinumab compared with placebo in patients with nonsegmental vitiligo (e.g., patients having: 1) moderate to extensive vitiligo (body surface area involvement $\geq 3\%$); 2) active vitiligo (a - clear evidence of progression using digital pictures for follow-up (maximum time between the two observations = 7 months) and/or b - disease progression during the last six months (as reported by the patient) or at least one clinical activity sign (hypopigmented areas, vitiligo lesions with blurred borders or confetti-like depigmentations)); 3) vitiligo on hands and/or face; 4) fitzpatrick skin type 3-6; and 5) Impact score $> 8/10$ or DLQI (Dermatology Life Quality Index) > 10) in a proof-of-concept

study. 10-15 subjects suffering from generalized (non-segmental) vitiligo are screened for eligibility, their clinical symptoms are determined, and their disease is confirmed. A careful, complete standard history and physical exam is performed to assure uniform data collection on every subject. Vital signs, extent of skin involvement (e.g., percent depigmentation) and weight are obtained at each visit.

All study subjects receive either placebo or SC secukinumab at a dose of either 150 mg or 300 mg in one of the following regimens: weekly during week 0, 1, 2, 3 and then monthly beginning during week 4; or monthly (no induction regimen). The primary outcome, percent change in repigmentation with therapy as measured using the Vitiligo Area and Severity Index (VASI) score, is assessed at 24 weeks. Secondary outcome measures include percentage repigmentation with secukinumab therapy as measured using the physician's global assessment, effect on disease-related quality of life as measured using the validated Vitiligo Quality of Life (VitiQOL) tool, maintenance of repigmentation after stopping therapy, and initial time to repigmentation. Some patients may continue in an extension study, receiving the same dose of secukinumab at monthly intervals, with reassessment of skin involvement at week 52. Subjects completing the primary study who do not enter the extension study are monitored at a week 32 follow-up visit to evaluate maintenance of response (repigmentation). Subjects completing the extension study are monitored at a week 60 follow-up visit to evaluate maintenance of response (repigmentation).

During the primary study, based on the Investigator's clinical judgment, a dose escalation to 300 mg may be implemented if, after, e.g., 12 weeks of dosing at 150 mg, a subject has not experienced repigmentation or escalation is warranted based on persistent signs and/or symptoms of disease. Following any dose escalation, subjects will be observed for 4 weeks; if criteria for dose escalation are still met, the dose may be raised again, e.g., to 350 mg SC or 450 mg once-monthly.

WHAT IS CLAIMED IS:

1. A method of treating vitiligo, comprising administering an IL-17 antibody or antigen-binding fragment thereof to a patient in need thereof, wherein the IL-17 antibody or antigen-binding fragment thereof binds to an epitope of a human IL-17 homodimer having two mature human 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 or antigen-binding fragment thereof has a K_D for human IL-17 of about 100-200 pM, and wherein the IL-17 antibody or antigen-binding fragment thereof has an *in vivo* half-life of about 4 weeks.
2. The method according to claim 1, wherein the patient has a concomitant autoimmune disease, such as psoriasis.
3. The method according to claim 1 or 2, wherein the patient has generalized or non-segmental vitiligo.
4. The method according to any of the above claims, further comprising administering to the patient a steroid, an antibiotic, or a TNF-alpha antagonist.
5. The method according to any of claims 1 to 4, comprising administering the patient about 150 mg of the IL-17 antibody or antigen-binding fragment thereof by subcutaneous injection at weeks 0, 1, and 2, followed by once monthly dosing starting at week 4.
6. The method according to any of claims 1 to 4, comprising monthly administering the patient about 150 mg of the IL-17 antibody or antigen-binding fragment thereof by subcutaneous injection.
7. The method according to any of claims 1 to 4, comprising monthly administering the patient about 300 mg of the IL-17 antibody or antigen-binding fragment thereof by subcutaneous injection.

8. The method according to any of claims 1 to 4, comprising administering the patient about 300 mg of the IL-17 antibody or antigen-binding fragment thereof by subcutaneous injection at weeks 0, 1, 2 and 3, followed by once monthly dosing starting at week 4.

9. The method according to any of the above claims, wherein the IL-17 antibody or antigen-binding fragment thereof comprises:

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

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

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

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

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

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

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

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;

ix) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14;

x) an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15; or

xi) an immunoglobulin light chain comprising the amino acid sequence set forth as SEQ ID NO:14 and an immunoglobulin heavy chain comprising the amino acid sequence set forth as SEQ ID NO:15.

10. The method according to any of the above claims, wherein the IL-17 antibody or antigen-binding fragment thereof is secukinumab.

11. A method of treating a patient having vitiligo, comprising administering the patient about 150 mg or about 300 mg of secukinumab by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by monthly dosing.

12. The method according to any of the above claims, wherein the patient has moderate to extensive vitiligo.

13. The method according to any of the above claims, wherein the patient has active vitiligo.

14. The method according to any of the above claims, wherein the patient has $\geq 3\%$ body surface area (BSA) involvement, preferably $\geq 15\%$ BSA involvement.

15. The method according to any of the above claims, wherein the patient experiences at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or 100% repigmentation after 36 weeks of treatment.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053701A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/24
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	D. A. BASSIOUNY ET AL: "Role of interleukin-17 in the pathogenesis of vitiligo", CLINICAL AND EXPERIMENTAL DERMATOLOGY, vol. 36, no. 3, 24 December 2010 (2010-12-24), pages 292-297, XP055401655, GB ISSN: 0307-6938, DOI: 10.1111/j.1365-2230.2010.03972.x abstract, page 294-295, in particular page 295, right-hand col., last paragraph ----- -/--	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

1 September 2017

Date of mailing of the international search report

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Bernhardt, Wiebke

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053701

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Information on patent family members

International application No

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